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Research report

Internally vs. externally triggered movements in patients with major depression

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ABSTRACT

Background: Psychomotor retardation is a prominent clinical feature of major depression. While several studies investigated these deficits, differences between internally and externally triggered response selection and initiation are less well understood. In the current study, we delineate internally vs. externally driven response selection and initiation in depression and their relation to basic psychomotor functioning.
Methods: 20 inpatients diagnosed with a (unipolar) major depression and 20 closely matched healthy controls performed a computerized motor paradigm assessing differences between internally and externally cued movements. Psychomotor performance and basic memory functions were assessed using a neuropsychological test-battery. To examine within group homogeneity a multivariate clustering approach was applied.
Results: Patients featured a global slowing of internally and externally cued response selection compared to controls, as well as impairments in basic psychomotor functioning. Yet, basic motor speed was preserved. Furthermore, patients were more severely impaired when movements involved internal response selection. The data-driven clustering revealed two patient subgroups, which both showed psychomotor disturbances, while only one featured slowing of response selection.
Interpretation: The results suggest a differential rather than a global psychomotor slowing in major depression with specific impairments of visuospatial and attentional processing as cognitive aspects of psychomotor functioning. As found for depression, in Parkinson's disease internally cued movements are more severely affected than externally cued reactions. Both may therefore be caused by dopaminergic deregulation due to frontostriatal deficits. Finally, multivariate clustering of behavioral data may be a promising future approach to identify subtypes of psychomotor or cognitive disturbances in different patient populations.

1. Introduction

Psychomotor disturbances (PMD) are considered a common symptom of major depression that is often already evident in the first clinical contact with a patient. Together with frequently observed cognitive deficits, psychomotor retardation form the core of non-affective symptoms of depression [1,2]. These non-affective symptoms may severely impact on patients' psychosocial functioning [3–5] but also pose challenges to treatment regimens that requite active participation of the patient, in particular psychotherapeutic intervention. Hammar and Ardal [4] reviewed the literature on cognitive functioning in major depressive disorder over the past decade and concluded that depression is not only associated with cognitive impairments in the acute phase of illness. Rather these cognitive, in particular attentional and mnemonic deficits [6–8] may persist despite recovery from affective symptoms [9,10]. In case of psychomotor symptoms, however, the relation to depression severity remains in question [11]. In a recent meta-analysis McDermott and Ebmeier [12] reported significant correlations of depression severity with disturbances not only of episodic memory and executive functions but also processing speed. They furthermore examined the influence of psychomotor retardation on cognitive deficiencies by comparing psychomotor speed related (timed) and unrelated (untimed) subtests of cognitive functions. From this comparison, they concluded that psychomotor retardation is not responsible for depression severity related cognitive deficits.

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In a pioneering review on psychomotor symptoms in depression, Sobin and Sackeim [1] emphasized the significance of motor disturbances as a core symptom of this disorder and concluded that these are a strong marker for the melancholic subtype. Based on this work, Schrijvers et al. [13] reviewed subsequent studies of PMD and distinguished three subdomains of psychomotor functions: speech, gross and fine motor activity.

The construct 'psychomotor' necessarily encompasses cognitive and motor aspects of motor control [i.e., planning, programming and execution (cf. [13])]. To investigate which aspects are specifically affected in major depression several studies employed computerized drawing tasks manipulating the cognitive effort necessary for task completion. The cognitive load is rather small in simple line drawing [14–17] and increases with complexity of the template in figure copying [15,16,18–20]. In this approach, movement duration represented the motor aspect while the time to initiate drawing was considered the more cognitive aspect of fine motor activity. Overall, these studies demonstrated that both the motor and the cognitive aspect of psychomotor functioning are slowed in medicated as well as non-medicated depressed patients, regardless of age. There is also good evidence for a depression related slowing in simple choice reaction tasks, which was repeatedly demonstrated using visual cued response selection [21–23].

Some of these features of psychomotor slowing in depression resemble bradyphrenia in Parkinson's disease [24–26]. A main characteristic of parkinsonian bradykinesia is the difficulty to initiate movements in absence of an external cue rather than a general motor slowing [26,27]. This prompted Rogers [28] to propose the hypothesis of dopaminergic deregulation due to frontostriatal deficits as a general mechanism for psychomotor changes in psychiatric and neurologic diseases such as (melancholic) depression, schizophrenia, dementia or Parkinson's disease [29]. Major depression was repeatedly associated with disturbances of the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC) and the basal ganglia (BG) [28,30,31]. Supporting Roger's hypothesis, the investigation of internally specified and externally cued movements again resemble prefrontal hypoactivation in Parkinson's disease [32] and catatonic schizophrenia [33]. Based on these considerations, the aim of the current study was now to delineate PMD for internally vs. externally driven response selection and initiation as aspect of (fine) motor control in major depression. Furthermore, cognitive and motor aspects of PMD should be largely independent of current disease severity [12]. To test these hypotheses, subjects completed a computerized response selection paradigm and further assessment of basic psychomotor functioning in the fine motor domain.

2. Materials and methods

Twenty patients with unipolar depression [diagnosis according to the ICD-10: F32.X, F33.X [34]] as well as twenty age-, sex-, handedness and (own and parental) education matched healthy controls were enrolled in our study. Depressive symptom severity was diagnosed with the ICD-10 and the German version of the revised Beck Depression Inventory-2 [BDI-2 [35]]. All examined patients were inpatients in the RWTH Aachen University Hospital at the time of testing and diagnosed by the attending doctors with major depression (F32) or an acute episode of a recurrent depressive disorder (F33) according to ICD-10 [34]. Any comorbid psychiatric or neurological diseases including alcohol or drug abuse was an exclusion criterion. It was assessed by the attending psychiatrist (in patients) and additionally by a structured clinical interview using the German version of the SCID inventory [36] in patients and also in controls to exclude a history of psychiatric and neurologic diseases. The minimum age for inclusion was 18 years. As we did not introduce an age limit in order to also include older patients, we screened for dementia using the Mini Mental State Examination [MMSE (Folstein [37])] with a cut-off at 23. Benzodiazepine medication was an exclusion criteria, because it is well known to induce cognitive and psychomotor impairments [38]. Socio-economic status was assessed using a structured interview. A comprehensive description of the patient group including antidepressant medication and dose is given in Table 1. All but one patient were right-handed according to the Edinburgh handedness inventory [39]. All subjects including healthy controls gave informed written consent to the study protocol, which had been approved by the local ethic committee of the RWTH Aachen University Hospital.

First, all participants were screened with a structured interview assessing socio-economic status and excluding comorbidity in patients as well as history of psychiatric and neurologic diseases in controls. Then, qualified subjects completed our computerized motor paradigm assessing differences between internally and externally specified reactions. A brief training ensured adequate task comprehension. The paradigm consisted of two parts lasting 16 min each. Subsequently, a neuropsychological test battery was conducted, followed by the self-report questionnaire of depressive symptoms (BDI-2) and a short debriefing. During examination participants and patients in particular were allowed to pause in between single tests taking as much time as needed. Altogether data acquisition took between 1.5 and 2 h per subject.

2.1. Motor paradigm

The experimental motor task consisted of unilateral button presses performed with the right or left index finger assessing differences between internally and externally specified reactions in three different conditions: (1) a *Free choice* of button presses with the left or right hand at a self-chosen point in time, (2) a *Timed choice* task, when the time of movement was cued by a visual stimulus but the hand to be moved was chosen by the subject, or (3) a *Reactive* task when laterality and time of movement were both cued by a visual stimulus.

2.1.1. Free choice: self-timed movement selection (free timing/choice of hand)

In the '*Free*'-condition the movements were entirely self-initiated. The subjects were instructed to press one of the two buttons at any self-chosen time. Every response was immediately followed by a 3.5 s visual feedback consisting of an arrow pointing to the side of the button-press. During the feedback no further responses were allowed to prevent sequential finger tapping. When training the subjects, they were explicitly instructed to vary the inter-stimulus intervals as well as the hand used in order to prevent rhythmic responses or any kind of movement routine. The time intervals between single responses were recorded on-line and subsequently used as inter-stimulus intervals (ISI) for the visual cued responses in the other two conditions. Likewise, the frequency of right and left button-presses was fed back as visual cues triggering a lateralized response in the '*Reactive*'-condition.

2.1.2. Timed choice: spatial choice at a cued time-point (external timing/choice of hand)

In the '*Choice*'-condition, stimuli consisted of arrows pointing to both sides presented for 3.5 s. The task was to respond as fast as possible by pressing either the left or right button. Subjects were free in choosing the side of response, but should vary between left and right sided responses. The ISIs and thus the number of button presses from the preceding '*Free*'-condition were presented in a random sequence to assure comparability of motor responses timing between conditions.

2.1.3. Reactive: reaction to a lateralized stimulus (external timing/cued hand)

In contrast to the '*Choice*'-condition, responses in the '*Reactive*'-condition were fully predetermined by the visual cue. Subjects had to react as fast as possible to a single-headed arrow pointing to the left or right by pressing the corresponding button. Like in the '*Choice*'-condition, ISIs and lateralization of responses were matched to the preceding '*Free*'-condition.

In summary, each ISI generated by a subject in the '*Free*'-condition was subsequently used to trigger one response both in the subsequent '*Choice*'- and '*Reactive*'-condition. The experiment consisted of 2×12 blocks of conditions, and lasted approximately 33 min. By randomizing ISIs in the '*Choice*'-condition and ISI and number of left and right responses (independently) in the '*Reactive*'-condition, anticipation confounds with respect to cue sequences were avoided, while comparability across conditions was preserved. For each condition 8 blocks of 60 s duration were presented in sequences of either 1 ('*Free*')–2 ('*Choice*')–3 ('*Reactive*') or 1–3–2 in the same pseudo-randomized order. The entire experiment lasted approximately 30 min including 5 s breaks between the blocks.

2.2. Psychomotor and cognitive assessment

All subjects completed a test battery assessing basic psychomotor and cognitive functioning.

2.2.1. Finger tapping

Subjects were asked to perform tapping movements as rapidly as possible for 10 s using the left or right index finger. Median number of taps from 3 trails per hand (separated by short breaks to prevent muscular fatigue) was used as the test score assessing basic motor speed.

2.2.2. Pointing movements

Subjects performed rapid horizontal pointing movements between two spots 30 cm apart using the right or left index finger [cf. CAPSIT Parkinson's disease test battery [40]]. Subjects were instructed to perform the movements as quickly and accurately as possible in three trials of 10 back-and-forth pointing movements. Median number of 3 trails per hand represented basic motor coordination.

Table 1
For all 20 patients age, gender, education (in years at school and university), parental education, diagnose according to ICD-10, self-reported symptom severity according to the revised Beck Depression Inventory (BDI-2), type and dosage of medication at the time of examination and subgroup cluster are listed (SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; NDRI: norepinephrine–dopamine reuptake inhibitor; MAOI: monoamine oxidase inhibitor; TeCA: Tetracyclic antidepressant; TCA: Tricyclic antidepressant). Diagnoses of F32.x indicate a first major depressive episode, those of F33.x a major depressive episode of a recurrent depressive illness. The last digit codes the (clinical) severity with F3x.0 indicating a mild, F3x.1 a moderate, F3x.2 a severe episode without and F3x.3 a severe episode with psychotic symptoms. Cluster refers to the groups the patient was assigned to in the subsequent cluster analysis (cf. Fig. 1).

Age	Gender	Education (a)	Parental education	Diagnose (ICD-10)	BDI-2	Medication (mg/d)				Patient cluster
						SNRI/*SSRI	TeCA/*TCA	Atypical-/*antipsychotics	Anticonvulsants/*Hypnotics	
18	Male	11	16	F32.0	25	Nil				2
19	Female	12	9	F33.2	23	[NDRI: Bupropion 300]				1
26	Female	10	8	F32.1	48	Duloxetine 60	Mirtazapine 7.5			1
32	Female	12	18	F33.1	37	Venlafaxine 300	*Trimipramine 50	Quetiapine 800, Risperidone 4 *Pipamperone 40		2
33	Female	10	9	F32.1	23	Venlafaxine 225		Quetiapine 200		1
36	Female	12	8,5	F32.1	43	*Citalopram 20	Mirtazapine 15			1
40	Female	9	9	F32.0	16	Nil				1
42	Female	17	13	F32.2	2	*Citalopram 40				1
46	Female	10	–	F33.2	37	Duloxetine 120			Pregabalin 300, *Zopiclone 7,5	1
47	Male	10	7.5	F33.1	29	Duloxetine 60	Mirtazapine 45		Pregabalin 225	2
48	Female	18	9	F33.1	31	Duloxetine 120	Mirtazapine 15			2
50	Male	9	8	F32.1	31	Duloxetine 60			Pregabalin 900	1
52	Male	9	8	F32.3	34	Venlafaxine 150		Risperidone 1		1
52	Female	10	10	F33.1	25	Duloxetine 120			Pregabalin 50	2
53	Male	11	-	F33.2	18	Duloxetine 60			Pregabalin 150, *Zolpidem 5	1
55	Male	12	9	F32.1	6	Venlafaxine 150				1
56	Female	11	11	F32.1	12	Venlafaxine 225				2
67	Male	8	8	F33.1	27	[MAOI: Tranylcypromine 70]	Quetiapine 300	Lamotrigine 150, *Zopiclone 7,5	1	
69	Female	8	8	F33.1	12	Duloxetine 60		*Pipamperone 40		1
71	Female	8	8	F32.3	17	Venlafaxine 225	*Trimipramine 50*	Risperidone 3		2

2.2.3. Trail making test

The two classical versions of the Trail Making Test [41] were used to assess attention as well as visuomotor speed (TMT-A) and cognitive flexibility (task-switching in TMT-B). The task consisted in consecutively connecting numbered circles (TMT-A) or switching between numbers and letters (TMT-B). Longer times indicate poorer performance.

2.2.4. Digit span subtest of the Wechsler Adult Intelligence Scale [42]

The verbal reproduction of an auditory presented digit span forwards and backwards were measured as markers for immediate memory (digit span forward, DS-F) and working memory performance (digit span backward, DS-B).

2.2.5. Multiple-choice vocabulary intelligence test

For an estimate of crystalline intelligence, a multiple-choice vocabulary intelligence test [MWT-B [43]] was used. The task consisted in making one actual word among four pseudo-words with increasing difficulty without time limitation.

2.3. Data analysis

All measurements were analyzed for group differences by means of a Wilcoxon–Mann–Whitney two-sample rank-sum test using MATLAB (Mathworks, Natick, MA). This non-parametric test was chosen as data (in particular the raw test-scores) did not fulfill the criteria for parametric testing, i.e., normal distribution. Due to their greater robustness against outliers, medians rather than means of test scores and measured values are reported. To test for relationships between psychomotor and cognitive performance Spearman's rank correlation coefficients were computed over all obtained measures. The test scores were also correlated with depressive state (symptom severity) as reflected by the ICD-10 diagnosis [34] and the BDI-2 [35].

Possible influences of antidepressant medication on test results were estimated by computing correlations between test scores and on-off state of each drug. To examine homogeneity within the patient group a spectral reordering approach (Johansen-Berg et al. [44]) was applied to assess whether patients may be clustered into subgroups with distinct cognitive-motor performance. This approach involves first to compute a cross-correlation matrix of the measures of cognitive and motor performance obtained for the individual patients. The matrix is then reordered to minimize the weight of cross-correlation values off the diagonal, hereby forcing highly correlated patients close towards each other. Clusters may then be identified in the reordered matrix as sets of patients whose cognitive-motor profiles were strongly correlated with each other and weakly with the rest of the matrix. The association between patient subclusters with diagnosis (first episode, recurrent episode) or with the different types of antidepressant treatment was assessed with Fischer's exact test.

3. Results

3.1. Clinical characteristics

Patients and healthy controls were not different in terms of age (median: patients 47.5 years vs. controls 49 years, rank-sum test: $p = 0.787$), handedness (lateralization quotient: 95.7 vs. 100, $p = 0.733$), education (10.0 years vs. 10.5 years, $p = 0.466$) and parental education (9.0 years vs. 9.0 years, $p = 0.829$). Among the 20 patients, half were diagnosed with recurrent depression, the other half with an isolated (or first) depressive episode. The majority (12) were treated for moderate depression, followed by severe (6) and mild (2) depression. Predictably, median scores in the standardized self-report scale of depressive symptoms BDI-2 were evidently higher in patients [25.0 (inter-quartile range: 16.0)] than in controls [0.0 (IQR: 1.5); $p < 0.0001$].

3.2. Motor paradigm

In both groups, the proportion of right and left button presses was approximately balanced in the 'Free'- (median proportion of right choices: patients 53.3% vs. controls 54.5%) and '*Choice*'-condition (55.2% vs. 55.1%). Importantly, the proportion of left/right responses did not differ between groups in either condition or between conditions in either group ($p > 0.483$ for all comparisons). Error rates could only be obtained in the '*Reactive*'-condition. There was no significant difference in the proportion of incorrect or missed responses between groups indicating equally good task performance [median error rates for patients 2.0% (IQR 6.6%) and for controls 1.2% (IQR 1.9%); $p = 0.407$].

Our experimental paradigm demonstrated a marked psychomotor slowing across all task conditions in the patient group (Table 1). In the '*Free*'-condition, patients initiated less responses by themselves than controls (medians: patients 83.5, controls 105.5; $p = 0.006$) and hence were slower to initiate new button presses ($p = 0.016$). In the '*Choice*'-condition, the slowing in the patient group was highly significant (medians: patients 588 ms, controls 407.5 ms; $p = 0.0003$). Patients also showed slower response times in the '*Reactive*'-condition (medians: patients 500.5 ms, controls 450.5 ms; $p = 0.048$). The fact that task performance, as indicated by error rates, was clearly not different between groups indicated that this slowing did not reflect a speed-accuracy-tradeoff. A group-by-condition interaction ($p = 0.001$) was found as patients with depression were significantly slower to respond in internally cued than in externally cued reactive trials (median difference: −42.0 ms), whereas control subjects were faster in the same comparison (median difference: +46.5 ms).

Finally, investigating the trial-by-trial variation in reaction times in the '*Reactive*'-condition revealed that there was a higher within-subject variability in the patient group (standard deviation [SD]: 104 ms) than in healthy controls (SD: 71 ms; $p = 0.006$). The same was true for the '*Choice*'- (SD: patients 156.5 ms, controls 126.5 ms; $p = 0.023$) and the '*Free*'-condition (SD: 1765.5 ms, 909.5 ms; $p = 0.008$). That is, depressive patients were less stable in their performance over the course of the 30 min experiment than controls even though no indication of gradual decline in performance was found suggestive of accelerated fatigue by inspection of the individual reaction time developments.

3.3. Psychomotor and cognitive assessment

Patients showed lower scores in all tests than healthy controls ($p < 0.008$ for all comparisons, see Table 2) except for finger tapping, hence, basic motor speed was the only variable not reduced in major depression ($p = 0.203$). With increasing cognitive involvement in the psychomotor tests, depressive patients took longer to perform pointing movements ($p = 0.002$) and were significantly slower to complete either version of the trail making test. They also showed a significantly lower digit span for both forward and backward reproduction, indicating short-term memory deficits. In spite of the fact that patients and controls were well matched (pair-wise matching of age and education ± 2 years) and did hence not differ with respect to age, own and parental education, the MWT-B as an estimate of crystalline intelligence was lower in the patient group (25.0 vs. 31.0 correct answers out of 37 items; $p < 0.001$). This apparent difference in intelligence can partially be explained by attention and especially memory deficiencies in major depression, in particular since only in patients we found a significant correlation of the MWT-B with immediate memory performance ($r = 0.56$; $p = 0.016$) assessed with DS-F.

3.4. Correlation with symptom severity and diagnosis

Among performance in the motor paradigm, only variation in reaction times in the '*Choice*'-condition showed a significant correlation with disease severity according to ICD-10 ($r = 0.46$; $p = 0.039$). That is, patients with worse clinical state performed less stable in selecting a reaction. Furthermore, reduced performance in the DS-B (testing working memory) was correlated with the severity of self-reported depressive symptoms as measured by the BDI-2 ($r = -0.53$; $p = 0.019$). The only significant correlation with the two diagnoses (first episode, recurrent episode) in our sample was found also for DS-B ($r = -0.60$; $p = 0.007$). This indicates that patient who suffered from a recurrent depressive episode and those who

Table 2
Results obtained from the test of psychomotor and cognitive functions (RT: response times; SD: standard deviation; ms: milliseconds). For each cell, median (across the diagnostic group) and interquartil-range (IQR) are provided.

Psychomotor functions	Depressed patients	Healthy controls	*p*-Value
'Reactive'-condition			
Median Response Times (ms)	500.5 (IQR: 183.5)	450.5 (IQR: 82.0)	0.048*
SD across trials (ms)	104.0 (IQR: 44.0)	71.0 (IQR: 36.5)	0.006*
Errors (%)	2.0 (IQR: 6.6)	1.2 (IQR: 1.9)	0.407
'Choice'-condition			
Median Response Times (ms)	588.0 (IQR: 176.5)	407.5 (IQR: 92.5)	0.000**
SD across trials (ms)	156.5 (IQR: 45.0)	126.5 (IQR: 37.0)	0.023*
'Free'-condition			
Median Number of Responses	83.5 (IQR: 27.3)	105.5 (IQR: 18.0)	0.006*
Median Response Times (ms)	2053.5 (IQR: 1439.0)	1282.0 (IQR: 907.0)	0.016*
SD across trials (ms)	1765.5 (IQR: 1287.5)	909.5 (IQR: 916.0)	0.008*
'Reactive' – 'Choice' in RT (ms)	-42.0 (IQR: 110.5)	46.5 (IQR: 54.0)	0.001**
Tapping (Basic motor speed)	46.5 (IQR: 7.5)	47.7 (IQR: 11.0)	0.203
Pointing (Motor speed/Coordination)	9.0 (IQR: 3.8)	6.0 (IQR: 2.3)	0.002**
TMT-A (Visuomotor speed, Attention)	27.2 (IQR: 16.8)	17.5 (IQR: 6.3)	0.000**
TMT-B (Cognitive flexibility, Attention)	60.0 (IQR: 50.3)	38.0 (IQR: 16.0)	0.001**
Cognitive functions			
DS-F (Immediate memory)	6.0 (IQR: 1.8)	7.0 (IQR: 2.5)	0.006*
DS-B (Working memory)	5.0 (IQR: 2.0)	7.0 (IQR: 3.0)	0.007*
MWT-B (Crystalline intelligence)	25.0 (IQR: 5.8)	31.0 (IQR: 6.0)	0.000**

TMT-A/B: trail making test version A/B; MWT-B: multiple-choice vocabulary test; DS-F: digit span forwards; DS-B: digit span backwards.
* Significance was assessed using a Wilcoxon–Mann–Whitney two-sample rank-sum test $p < 0.05$.
** Significance was assessed using a Wilcoxon–Mann–Whitney two-sample rank-sum test $p < 0.005$.

reported increased symptom severity had more severe working memory deficits. In that context, it is important to note, that there was no significant difference in self-report of symptom severity (BDI-2) between patients with an acute depressive episode and with a recurrent depressive disorder (rank-sum test; $p = 0.493$).

3.5. Correlation between tests

When correcting for multiple comparisons across the number of performed analyses, only the positive correlation between the time taken to complete the two versions of the trail making test (TMT-A, TMT-B; $r = 0.72$; $p < 0.001$) remained significant.

At an uncorrected level of $p < 0.05$, positive correlations between response times in the '*Reactive*'-condition and those in the '*Choice*'- ($r = 0.64$; $p = 0.003$) and 'Free'-condition ($r = +49$; $p = 0.031$) was observed along with a trend towards a correlation between the latter variables ($r = +42$; $p = 0.067$). A negative correlation between finger tapping performance and response times in the '*Reactive*'-condition ($r = -.49$; $p = 0.027$), indicated that patients with faster basic motor speed featured lower reaction times and were hence faster to respond. To follow up this potential confound, a post hoc test was performed to control for the influence of basic motor speed on group differences in the experimental task. More specifically, finger tapping performance was introduced as a covariate in the analysis of group differences with respect to errors and response times in all three conditions. These subsidiary analyses replicated all results obtained above, suggesting that inter-individual differences in basic motor speed did not influence the group comparison.

3.6. Identifying clusters of patients

While the results above were based on correlating psychomotor and cognitive measurements over patients, the final exploratory analysis was based on the correlation between patients over all obtained scores. Spectral reordering of the computed cross-correlation matrix revealed a subdivision of the patient group into 2 distinct clusters, i.e., subgroups, consisting of 13 and 7 patients, respectively (Fig. 1).

While performance of patients within each subgroup was closely correlated, correlation with the respective other group was low. Notably, these two subgroups did neither differ with respect to age ($p = 0.832$), own or parental education ($p = 0.801$; $p = 0.774$) nor depression severity (ICD-10 mean: cluster 1.38 = 1, group 2 = 1.14; $p = 0.393$; BDI-2: 23.0, 25.0; $p = 0.893$) or number of antidepressant agents ($p = 0.620$). The clustering seemed thus not a mere reflection of age, education, clinical status or quantity of medication. There also was no association between subgroup and diagnosis (first episode, recurrent episode) according to Fischer's exact test ($p = 0.642$). When the deficits of each group were delineated by comparison to the healthy controls, both groups featured significantly lower scores in almost all neuropsychological tests ($p < 0.039$ for all comparisons but for DS-F $p = 0.06$ in the smaller group, see Table 2), while error rate and basic motor speed were not different from the controls in either group. However, only the larger cluster showed pronounced PMD evident by slower response times in the '*Choice*'-condition ($p < 0.001$) as well as higher inter-subject variability in the '*Choice*'- ($p = 0.004$) and the '*Reactive*'-condition of the motor paradigm ($p = 0.001$). Therefore, patient of this subcluster were significantly slowed in the internal selection of a reaction relative to purely reactive trials (median difference: −64.0 ms) (Table 3).

3.7. Medication and correlation with test performance

The respective medication of every patient is documented in Table 1. Only 2 patients did not receive any medication while the majority was treated with a combination of antidepressants. The most common activating drug were serotonin–norepinephrine reuptake inhibitors (SNRI) in 14 of 20 patients, that is 8 received Duloxetin [average daily dose (ADD): 83 mg], 6 Venlafaxine (ADD: 213 mg) and additional 2 patients received the selective serotonin reuptake inhibitor (SSRI) Citalopram (ADD: 30 mg). 6 patients were treated with rather sedating Tetracyclic (TeCA) or Tricyclic antidepressants (TCA), more precisely 4 patients received Mirtazapine (ADD: 21 mg) and 2 patients Trimipramine (ADD: 50 mg). Moreover, 6 patients were treated with diverse antipsychotics and 6 with anticonvulsants of which 5 patients received Pregabalin (ADD: 325 mg). Importantly, there was no statistical association between subgroups and any type of medication (Fischer's exact test, SNRI/SSRI: $p = 1$; TeCA/TCA: $p = 0.122$; Antipsychotics: $p = 1$; Anticonvulsants: $p = 1$; Hypnotics: $p = 0.521$).

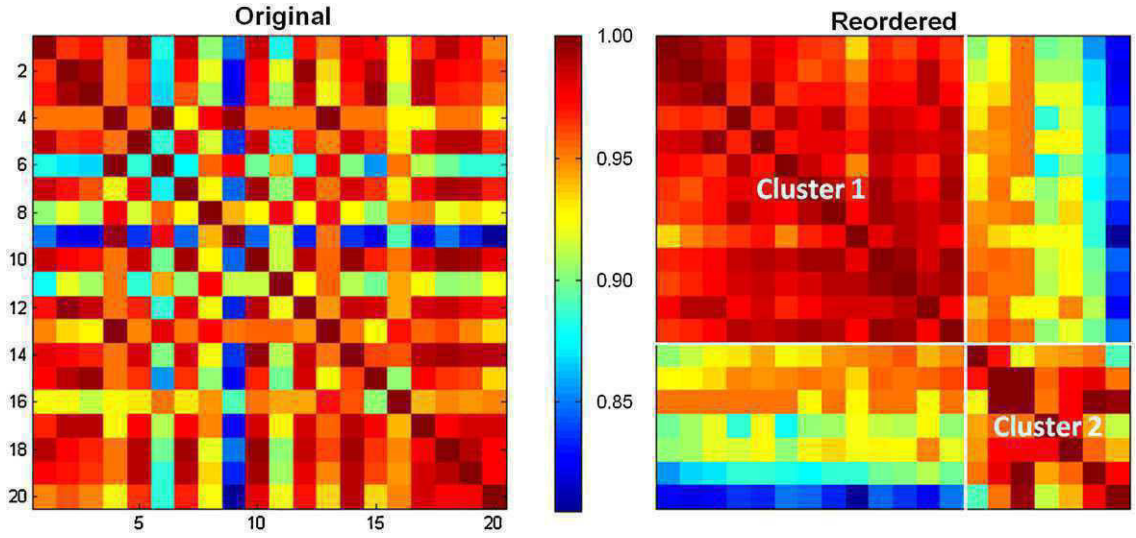

Fig. 1. (Original) Cross-correlation matrix obtained by the hierarchical cluster analysis (color coding of correlation between patients) linking patients on base of their overall similarity in psychomotor and neuropsychology measurements. (Recordered) Spectral reordering of the cross-correlation matrix [57] yields two clusters of higher inter-correlation between the first 13 patients in Cluster 1 and the next 7 in Cluster 2.

When analyzing the statistical relationship between medication and test results, no association was found between medication and performance in the motor paradigm. In contrast, the treatment with SNRIs/SSRIs featured a negative correlation with time for pointing movements ($r = -0.46$; $p = 0.041$) indicating faster basic motor coordination with SNRI medication. TeCAs/TCAs prescription correlated negatively with finger tapping ($r = -0.46$; $p = 0.044$) and positively with pointing performance ($r = 0.52$; $p = 0.019$) suggesting slower basic motor speed and coordination with TeCAs/TCAs treatment in 6 patients. Finally, administration of typical or atypical antipsychotics correlated positively with both trail making test scores (A: $r = 0.66$; $p = 0.001$; B: $r = 0.57$; $p = 0.009$) and negatively with DS-B ($r = -0.45$; $p = 0.044$). This suggests that antipsychotic treatment affected cognitive functioning, i.e., attention and working memory in 6 patients.

4. Discussion

The present study investigated psychomotor functioning in the fine motor domain in patients with unipolar major depression. Comparing internally and externally cued response selection and initiation, patients were particularly slowed when movements involved internal movement selection. A data-driven clustering approach revealed a tendency towards two distinct subgroups. While both featured consistent impairments in fine motor functioning, only one subgroup showed significant disturbances in response selection and initiation.

4.1. General and specific psychomotor disturbances

In our experimental motor paradigm we replicated the finding that depressed patients are significantly impaired in reaction speed

Table 3
Results obtained from the comparison of psychomotor and cognitive performance of healthy controls with each of the two patient subgroups derived from the clustering approach (cf. Fig. 1; RT: response times; SD: standard deviation; ms: milliseconds). For each group, median (across the diagnostic group) and interquartil-range (IQR) are provided.

Psychomotor	Healthy controls	Patient cluster 1	*p*-Value	Patient cluster 2	*p*-Value
'Reactive'					
Median RT (ms)	450.5 (IQR: 82.0)	487.0 (IQR: 197.8)	0.135	514.0 (IQR: 168.0)	0.072
SD (ms)	71.0 (IQR: 36.5)	105.0 (IQR: 30.0)	0.004**	85.0 (IQR: 49.3)	0.159
Errors (%)	1.2 (IQR: 1.9)	2.8 (IQR: 9.8)	0.283	1.4 (IQR: 3.7)	0.945
'Choice'					
Median RT (ms)	407.5 (IQR: 92.5)	624.0 (IQR: 132.8)	0.000**	507.0 (IQR: 178.8)	0.114
SD (ms)	126.5 (IQR: 37.0)	169.0 (IQR: 24.8)	0.001**	123.0 (IQR: 39.3)	1.000
'Free'					
Median Responses	105.5 (IQR: 18.0)	82.0 (IQR: 18.0)	0.008*	92.0 (IQR: 44.5)	0.346
Median RT (ms)	1282.0 (IQR: 907.0)	1809.0 (IQR: 1234.8)	0.022*	2298.0 (IQR: 2073.8)	0.134
SD (ms)	909.5 (IQR: 916.0)	1627.0 (IQR: 1212.5)	0.016*	1905.0 (IQR: 1760.0)	0.063
'Reactive' – 'Choice'	46.5 (IQR: 54.0)	−64.0 (IQR: 115.3)	0.000**	38.0 (IQR: 41.8)	0.695
Tapping	47.7 (IQR: 11.0)	46.5 (IQR: 6.9)	0.294	46.5 (IQR: 8.1)	0.321
Pointing	6.0 (IQR: 2.3)	7.3 (IQR: 3.8)	0.039*	10.1 (IQR: 2.1)	0.000**
TMT-A	17.5 (IQR: 6.3)	27.3 (IQR: 12.8)	0.000**	25.8 (IQR: 20.6)	0.002**
TMT-B	38.0 (IQR: 16.0)	59.0 (IQR: 51.8)	0.002**	76.0 (IQR: 54.9)	0.011*
Cognitive					
DS-F	7.0 (IQR: 2.5)	6.0 (IQR: 2.0)	0.009*	6.0 (IQR: 2.5)	0.061
DS-B	7.0 (IQR: 3.0)	5.0 (IQR: 2.5)	0.033*	5.0 (IQR: 1.5)	0.022*
MWT-B	31.0 (IQR: 6.0)	24.0 (IQR: 7.3)	0.001**	25.5 (IQR: 7.0)	0.023*

TMT-A/B: trail making test version A/B; MWT-B: multiple-choice vocabulary test; DS-F: digit span forwards; DS-B: digit span backwards.
* Significance between groups was assessed using a Wilcoxon–Mann–Whitney two-sample rank-sum test $p < 0.05$.
** Significance between groups was assessed using a Wilcoxon–Mann–Whitney two-sample rank-sum test $p < 0.005$.

and response selection based on external cues [21–23]. Moreover, the internal selection of responses ('*Choice*'-condition) was markedly slowed in relation to matched controls. Finally, depressed patients also showed significantly fewer self-initiated movements ('*Free*'-condition), suggesting that not only the choice of a movement but also the drive to initiate movements is reduced. This congruency in all three aspects, which is echoed by the correlation of the respective response times, thus conforms to the known general impairment of psychomotor functions in major depression [2,13].

In contrast, finger tapping performance was not significantly impaired in our patient sample, which indicates that there was no deficit in basic motor speed. Yet, slowed finger tapping performance was found previously in depressed patients [45]. This divergence to our results may be attributable to the administration of SNRIs or SSRIs in 16 out of 20 patients in our sample. It has been shown that with this medication finger tapping performance does not differ from healthy controls [46] and even that psychomotor functioning generally ameliorated significantly with SSRI treatment [47,48]. Taken together with slowed reaction times and the increased time taken to complete the pointing movements and the trail making tests, this points to specific impairments of cognitive rather than motor aspects of psychomotor functioning. This corresponds well to known impairments of visuospatial and attentional processing in major depression [6,49–52]. Even though antipsychotic medication affected cognitive functioning and in particular attention, excluding the respective 6 patients form the comparison still revealed inferior performance in the trail making tests.

4.2. Deficient response selection and initiation

The most prominent finding of our study was that patients were markedly more slowed in internally triggered (non-cued) than in externally triggered (visually cued) reactions. The same symptoms are found in Parkinson's disease [27,53]. This specific deficit of (fine) motor control may be attributed to known disturbances in cognitive control centers, like the DLPFC, the rostral cingulate zone (RCZ) of the ACC and the BG in major depression [28,30,31]. In line with this interpretation are several studies associating the very same areas with internal selection and initiation of movements in the healthy brain [54–57]). Consequently, our results give some support to the general symptom hypothesis [28,29] presuming that psychomotor changes in Parkinson's and (melancholic) depression are caused by dopaminergic deregulation due to frontostriatal deficits. Analyzing event-related potentials in severely depressed patients, Schrijvers [58] recently demonstrated a close relationship between psychomotor retardation and impeded action monitoring. Based on this finding, it was suggested that the same frontostriatal areas form a part of a network of higher-order executive systems involved in response selection, motor control and action monitoring. In this framework, the RCZ is proposed to account for selection of actions [59], which is supported by very recent imaging data provided by using the same motor paradigm as in the present study [56]. Hence, RCZ function should be specifically affected in depressed patients with deficient response selection and initiation.

4.3. Patient subcluster with differential psychomotor disturbances

When patients were clustered by their test performance, a tendency towards two subgroups of patients may be identified. Intriguingly, this subdivision was primarily driven by differences in the motor paradigm. Whereas both subgroups showed impairments in fine psychomotor functioning and short-term memory, only one patient cluster featured significant disturbances of internal selection and initiation of movements. Likewise, Pier [15] demonstrated PMD in patients with major depression using computerized drawing tasks. When differentiating between patients with and without melancholic features in the same study, both groups showed impairments of cognitive aspects of psychomotor activity, whereas only melancholic patients also featured slowing of motor aspects. In this context, it may be argued that internal cueing of responses represents a motor aspect of psychomotor functioning [24,28]. Accordingly, Rogers [22] reported marked deficits specifically in response selection in depressed patients with melancholic features. As melancholia was not assessed in our patient sample, it may only be speculated that the clustering result is a reflection of the presence of melancholic features in the subgroup with more pronounced PMD. In favor of this assumption is that psychomotor retardation is common in depression with melancholic features [11] and even is considered a diagnostic marker for melancholic depression [2,13].

4.4. Psychomotor disturbance, cognitive impairment and clinical state

In the literature, memory deficits are very consistently linked to depression severity [12,50]. Correspondingly, we found increased working memory deficits in patients reporting increased symptom severity (BDI-2) and also with a recurrent depressive episode. Furthermore, severely depressed patients (ICD-10) were less stable in performing internal response selection ('*Choice*'-condition). According to Schrijvers [13], this association between clinical state and PMD is primarily observed in melancholic depression. Given the rather coarse classification of objective clinical state by ICD-10 in this study, the relationship between deficient response selection and disease severity needs further investigation.

In summary, the current results replicate known (fine) PMD in patients with major depression and moreover indicate specific impairments of visuospatial and attentional processing as cognitive aspects of psychomotor functioning. In the present study we demonstrated for the first time more severely affected internally triggered than externally triggered response selection with both being slowed in major depression. Finally, a cluster analysis revealed two subclusters of PMD in our patient sample. Therefore, multivariate clustering of behavioral data may be a promising future approach to identify subtypes of cognitive or psychomotor impairments in patient populations.

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The "What" and "When" of Self-Initiated Movements

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The ability to generate intentional behavior is undeniably at the core of what makes us acting subjects. Intentional actions consist of at least 2 components (Brass M, Haggard P. 2008. The what, when, whether model of intentional action. Neuroscientist. 14:319–325.): choosing an appropriate behavior (what) and selecting the moment of execution (when). The aim of this study was to identify differing and overlapping neural networks underlying the "what" and "when" of intentional movement initiation. While scanned with functional magnetic resonance imaging, 35 healthy subjects performed self-initiated and reactive, that is, internally and externally triggered movements of the right or left index finger in 3 experimental conditions: 1) "Free Choice" (free timing: when/choice of hand: what), 2) "Timed Choice" (external timing/choice of hand: what), and 3) "No Choice" (external timing/cued hand). The what-component specifically employed the presupplementary motor area (SMA) and dorsal premotor cortex bilaterally. The when-network consisted of superior SMA together with insula and Area 44 bilaterally as well as bilateral anterior putamen, globus pallidus, and left cerebellum subcortically. These 2 components recruited different networks, pointing to a partially distinct neuronal realization of the relating functions. Finally, the more intentional components were involved, the higher was activity in the anterior midcingulate cortex, which highlighted its role in intentional initiation of behavior.

Keywords: anterior midcingulate cortex, fMRI, free movement timing, intentional motor control, movement selection

Introduction

Since the discovery of the "Bereitschaftspotential" preceding self-initiated movements by Kornhuber and Deecke (1965), neuronal activity relating to intentional movement generation has been a vital field of research. Based on recent findings, Brass and Haggard (2008) proposed a heuristic framework for the investigation of intentional action that distinguishes 3 major components: 1) a component related to the decision about which action to execute ("what"-component), 2) a component about when to execute an action ("when"-component), and 3) the decision about whether or not to execute an action ("whether"-component). In the experimental context, however, we face the contradiction between freedom of choice as experimental condition and the empirical dictum of maximized control over conditions. Thus, in an empirical context, we only may consider partly free decisions. A common strategy to examine the 3 components individually is to compare predetermined reactions with actions of a certain degree of freedom (what or when) or movement execution with inhibition of movement execution (whether; Haggard 2008). A second problem consists in the difficulty to reliably operationalize all 3 intentional components in the same experiment, which is necessary to account for possible interdependencies between components. It seems especially difficult to integrate the whether-component together with the other 2 (what and when) because in case of a decision against movement execution, there is no behavior to directly relate to. In that case, we have to rely on introspections of the subject about the what- and the when-component at the same time, which entail known problems related to subjective reports (e.g., inaccuracy of retrospection). Therefore, in the current study, we focused on the what and when of self-initiated movements.

Typically, intentional action is operationalized either as the choice between predefined movements (what) or as the selection of a time point (when) to execute an action. Two decades ago, the dorsolateral prefrontal cortex (DLPFC) and the SMA were associated with the free choice between responses (Frith et al. 1991; Playford et al. 1992) in experiments using positron emission tomography. Jahanshahi et al. (1995) examined brain function during cued and non-cued rhythmic button presses and found that the right DLPFC significantly differentiated self-initiated from externally triggered movements. Using the same paradigm with irregular timing, Jenkins et al. (2000) found additional activation in left DLPFC, pre-SMA, and the anterior midcingulate cortex (aMCC; Palomero-Gallagher et al. 2009; Shackman et al. 2011). Varying movement frequency and complexity in a similar functional magnetic resonance imaging (fMRI) experiment, Deiber et al. (1999) observed that self-initiated movements induced stronger activation specifically in pre-SMA and aMCC while movement sequences increased activity in the SMA proper. Lau, Rogers, Ramnani, et al. (2004) found only pre-SMA activity tightly associated with the free choice of a target, while DLFPC activity matched a "specified target"-condition. Whereas SMA is related to movement performance (Nachev et al. 2008), the DLPFC probably contributes to attentional or working memory processes rather than to preparation and initiation of the actual motion in self-initiated movements (Wiese et al. 2005, 2006). Taken together, the pre-SMA and the aMCC seem to represent neural correlates of intentional movement selection and action initiation.

Recent attempts to disentangle the what and when components of intentional actions described above, suggested

the interplay of different neuroanatomically dissociable subfunctions in voluntary action control (Mueller et al. 2007; Krieghoff et al. 2009). Mueller et al. (2007) deployed a paradigm demanding to press 1 of 2 buttons. The choice of a movement to execute could be made either internally or was determined by a visual cue. Importantly, the timing was prespecified (though not directly cued) in both conditions. In particular, movements had to be performed syncopated, that is, executed rhythmically at the midpoint between sets of visual pacing stimuli every 1.2 s. The results indicated that movement selection (what) is associated with activity of the aMCC. The further conclusion about the when-component, however, was based on indirect evidence. The authors reasoned the pre-SMA to be linked to movement timing or initiation because it is activated in both conditions requiring syncopated movement pacing. It has been shown before that the pre-SMA plays a role in this mode of movement initiation, as it is reliably activated when externally timed movements are not executed synchronized with the rhythmic cue (Mayville et al. 2002; Jantzen et al. 2004). Yet, the pre-SMA was repeatedly found to be involved in various aspects of selecting an action (what), such as the choice of a specific response (Lau et al. 2004; van Eimeren et al. 2006) or the initiation of different action sets, for example, sets of action–selection rules, as necessary for task switching (Rushworth et al. 2004). Krieghoff et al. (2009) combined the selection of the left or right hand to move (what) with the decision between 2 auditory cued time points for movement execution (when) in one paradigm to dissociate internal movement selection and timing. After an instruction cue indicating an internal or external what or when decision and a variable delay, 4 tones were presented with interstimulus intervals (ISIs) of 1 s. Subjects had to choose between the third and the fourth tone to execute either a cued or non-cued movement. The results indicated an involvement of the aMCC in movement selection and of the paramedian frontal cortex anterior and dorsal to pre-SMA in action timing. The analysis, however, was focused on instruction-related neural activity, that is, activity related to the cue indicating the internally specified response to be made shortly, assuming that both choices (what and when) are always made immediately (within 1 s) after cue presentation. This, however, represents a strong assumption. Moreover, due to this approach, the results may pertain more to activity due to the preparation for a decision that is about to be taken shortly rather than to the decision itself. Alternatively, as timing was not free but a choice between 2 possible time points, subjects may have chosen a cue which, however, is different from actual free timing of movement initiation. This consideration together with the fact that the inference was based on a post hoc signal strength analysis with a rather liberal threshold, considerably weakens the dissociation of the what- and when-component in this study.

The aim of the present study was to address the described shortcomings and thereby robustly compare the what- and when-component of intentional movement initiation. We examined 2 major aspects of intentional actions, namely internally triggered movement selection and initiation, by combining the free choice of the executed movements (what) with a free timing of movement execution (when) in the same paradigm. While maintaining direct comparability of self-initiated and reactive movements, we intended to delineate the nodes of possibly differing neural networks underlying the free choice of a movement and of when to perform it. We hypothesized both the pre-SMA and the aMCC to be involved in self-initiated movements and especially aimed to clarify whether there is a differential involvement of these 2 neuroanatomically dissociable brain areas in the selection and timing of movements. Furthermore, we hypothesized the basal ganglia to be particularly activated during internal timing of actions, which is suggested by previous work (Cunnington et al. 2002; Debaere et al. 2003; Francois-Brosseau et al. 2009) and by behavioral symptoms of basal ganglia damage in Parkinson's disease (O'Boyle et al. 1996).

Materials and Methods

Subjects

We examined 35 healthy volunteers (age range 21–62 years, mean age 35.9 ± 12.4 standard deviation [SD] years; 17 females) without any record of neurological or psychiatric disorders and normal or corrected-to-normal vision. All subjects gave informed written consent to the study protocol, which had been approved by the local ethic committee of the RWTH Aachen University. Right-hand dominance of the participants was established by means of the Edinburgh handedness inventory (Oldfield 1971).

Experimental Protocol

The experimental task consisted of unilateral button presses performed with the right or left index finger under 3 different conditions: 1) a free choice of button presses with the left or right hand at a self-chosen point in time (what and when), 2) a Timed choice task, when the time of movement was cued by a visual stimulus but the hand to be moved was chosen by the subject (what), or 3) a no choice task when laterality and time of movement were cued by a visual stimulus (reaction). Responses were recorded using MRI-compatible response pads (LumiTouch, Burnaby, Canada). All visual stimuli were presented using the "Presentation" software package (Version 14.1; Neurobehavioral Systems Inc., Albany, CA) and were displayed on a custom-built shielded thin film transistor screen at the rear end of the scanner visible via a mirror mounted on the head coil (14° × 8° viewing angle). In the experiment, task blocks of 60 s duration were periodically alternated with rest periods of black screen presentation for 15 s serving as implicit "baseline." Each task block was introduced by a one-word instruction presented for 1.5 s, which informed the subject which of the 3 conditions had to be performed in the upcoming block. All cues consisted of white arrows presented on a black screen in the central field of view. A fixation cross in the middle of the screen indicated an ongoing task in each of the 3 conditions (Fig. 1).

Free Choice—Self-Timed Movement Selection and Execution (Free Choice of Hand/Free Timing)

In the "Free"-condition, the movements were entirely self-initiated. The subjects were instructed to press 1 of the 2 buttons at any self-chosen time. Every response was immediately followed by a 3.5 s visual feedback consisting of an arrow pointing to the side of the button press. During the feedback, no further responses were allowed to prevent sequential finger tapping and to separate the events for the statistical analysis. When training the subjects, they were explicitly instructed to vary the ISIs as well as the hand used in order to prevent rhythmic responses or any kind of movement routine. The time intervals between single responses were recorded online and subsequently used as ISIs for the visual cued responses in the other 2 conditions. Likewise, the frequency of right and left button presses was fed back as visual cues triggering a lateralized response in the "No Choice"-condition.

Timed Choice—Movement Choice at a Cued Time Point (Free Choice of Hand/External Timing)

In the "Timed"-condition, stimuli consisted of arrows pointing to both sides presented for 3.5 s. The task was to respond as fast as possible by pressing either the left or the right button. Subjects were free in choosing the side of response but should vary between left- and right-

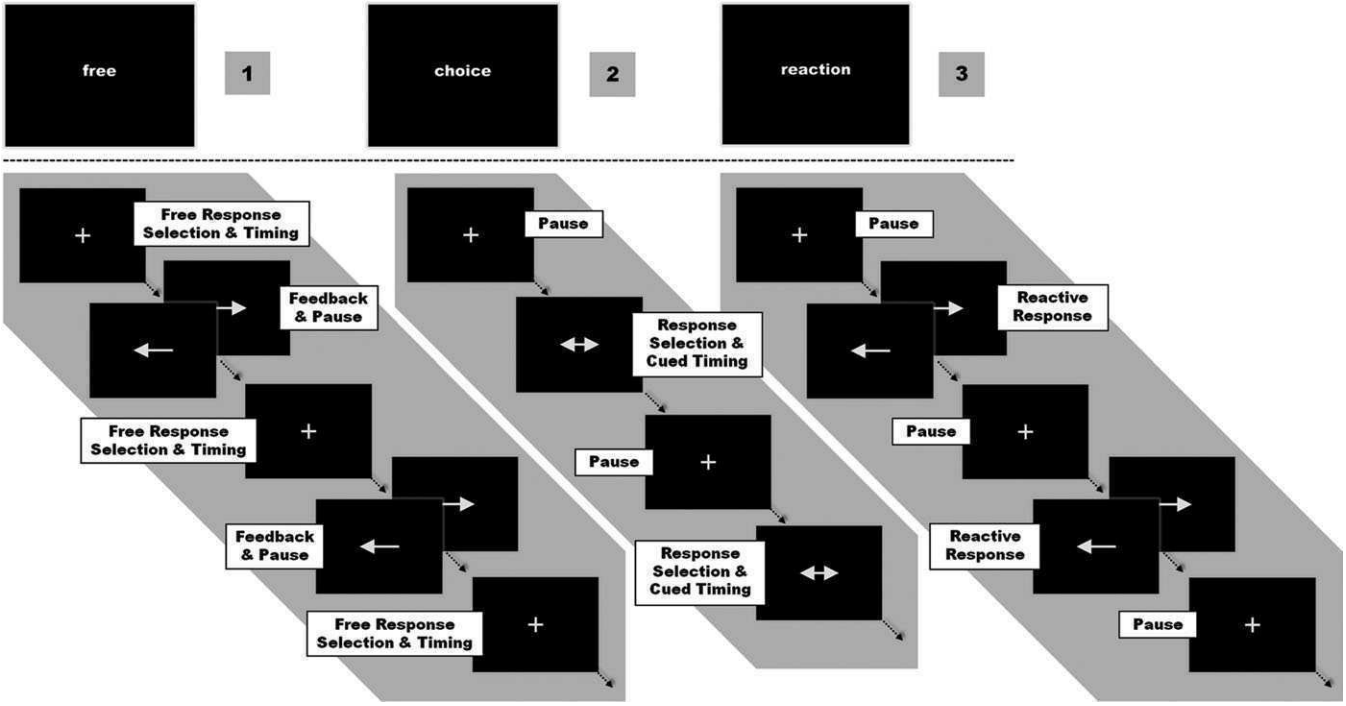

Figure 1. 1) [free] Choice, 2) Timed [choice], and 3) No Choice = [reaction]. Conditions were pseudorandomized in blocks of (1-3-2) or (1-2-3). Randomized ISIs and laterality of the beginning "Free"-condition determined the response cues in both the following "Choice"- and "No Choice"-conditions.

sided responses. The ISIs and thus the number of button presses from the preceding Free-condition were presented in a random sequence to assure comparability of motor responses timing between conditions.

No Choice—Lateralized Reaction (External Cue for Hand/External Timing)

In contrast to the "Timed Choice"-condition, responses in the No Choice-condition were fully predetermined by the visual cue. Subjects had to react as fast as possible to a single-headed arrow pointing to the left or right by pressing the corresponding button. Like in the Timed-condition, ISIs and lateralization of responses were matched to the preceding Free-condition.

In summary, each ISI generated by a subject in the Free-condition was subsequently used to trigger one response both in the subsequent Timed- and No Choice-condition. By randomizing ISIs in the Timed-condition and ISIs and number of left and right responses (independently) in the No Choice-condition, anticipation confounds with respect to cue sequences were avoided, while comparability across conditions was preserved. For each condition, 8 blocks were presented in alternating sequences of either 1 (Free)—2 (Choice)—3 (Reactive) or 1-3-2 in a pseudorandomized order. The sequences were spread evenly across the experiment session to minimize any potential confounds due to order effects. The whole experiment lasted approximately 33 min. We did not introduce a factorial 2 × 2 design with each the what- (hand) and when-component (timing) manipulated independently because this would have compromised the close comparability between conditions. The missing when-condition with free timing and cued hand would for instance have produced an additional set of ISIs. Also the visual input would not have been correlated with movements in that condition. This would have made a parallelization of timing parameters and visual input across conditions impossible.

Behavioral Data Analysis

Behavioral performance assessed during the fMRI experiment was analyzed offline using MATLAB (Mathworks, Natick, MA). The number of left and right button presses in the Free- and the Timed-condition across subjects were compared by means of paired *t*-tests using a statistical threshold of $P < 0.05$. Likewise, mean reaction times for correct responses were compared in the Timed- and the No Choice-condition using a paired *t*-test.

Functional Magnetic Resonance Imaging

Eight hundred and ninety two volumes were acquired on a Siemens Trio 3-T whole-body scanner (Erlangen, Germany) using a blood oxygen level-dependent (BOLD) contrast sensitive imaging sequence (gradient echo planar imaging [EPI], time repetition = 2.2 s, time echo = 30 ms, flip angle = 90°, in plane resolution = 3.1 × 3.1 mm, 36 axial slices, 3.1 mm thickness) covering the whole brain. Image acquisition was preceded by 4 dummy images allowing for saturation in T_2^* contrast. These images were discarded from further processing. The remaining 888 EPI images were analyzed using the SPM5 software package (www.fil.ion.ucl.ac.uk/spm). Images were first corrected for head movement by affine registration using a two-pass procedure, by which images were initially realigned to the first image and subsequently to the mean of the realigned images. After realignment, the mean EPI image for each subject was spatially normalized using the "unified segmentation" approach (Ashburner and Friston 2005). The resulting parameters of a discrete cosine transform, which defined the deformation field necessary to warp the subjects data into the space of the Montreal Neurological Institute (MNI) tissue probability maps, were applied to the individual EPI volumes and resampled at 2 × 2 × 2 mm^3 voxel size. The normalized images were spatially smoothed using an 8 mm full-width at half-maximum Gaussian kernel to meet the statistical requirements of the general linear model (GLM) and to compensate for residual intersubject variations in brain anatomy.

Statistical Analysis

The fMRI data were analyzed using the GLM as implemented in SPM5. Each response (button press) was modeled as an individual event for the left and the right hand in the 3 experimental conditions. The event-related input functions were then convolved with a canonical hemodynamic response function and its first-order temporal derivative to yield the final regressors. Including the temporal derivatives of the task regressors into the design has been shown to increase sensitivity

and specificity of the GLM by accommodating deviations of the BOLD timecourse from its canonical form (Josephs and Henson 1999; Henson et al. 2001). Parameter estimates were subsequently calculated for each voxel using weighted least squares to provide maximum likelihood estimators based on the temporal autocorrelation of the data (Kiebel and Holmes 2003). The first regressor for both hands in all 3 conditions represented the 6 simple main effects against the implicit baseline for every subject. These 6 individual first-level contrasts were then fed into a second-level group-analysis using an analysis of variance (ANOVA) employing a random effects model (Penny and Holmes 2003). We allowed for violations of sphericity by modeling nonindependence across images from the same subject and allowing unequal variances between conditions and subjects as implemented in SPM5.

Simple main effects of each task (vs. the resting baseline) as well as comparisons between experimental factors were tested by applying appropriate linear contrasts to the ANOVA parameter estimates. Conjoint main effects were tested by means of a conjunction analysis using the minimum statistics approach (Nichols et al. 2005). The resulting SPM(T) maps were then thresholded at $P < 0.05$ conducting a family-wise error (FWE) correction on the cluster-level (cluster forming threshold at voxel level $P < 0.001$; extend threshold: $k = 313$ voxels; Worsley et al. 1996). Anatomical assignment of the resulting activation clusters was achieved using the cytoarchitectonic maximum probability maps implemented in the SPM Anatomy toolbox (www.fz-juelich.de/ime/spm_anatomy_toolbox, V1.6; Eickhoff et al. 2005, 2007; Eickhoff, Heim, et al. 2006), which relies on previous studies that provided details about cytoarchitecture and intersubject variability of brain areas, such as Broca's Area (Brodmann area [BA]44, BA45; Amunts et al. 1999, 2004), premotor cortex (BA6; Geyer 2004), primary motor cortex (4a, 4p; Geyer et al. 1996), primary somatosensory areas (3a, 3b, 1, 2; Geyer et al. 1999, 2000; Grefkes et al. 2001), secondary somatosensory areas (OP1–4; Eickhoff, Amunts, et al. 2006; Eickhoff, Schleicher, et al. 2006), intraparietal sulcus (hIP1-3; Choi et al. 2006; Scheperjans, Eickhoff, et al. 2008; Scheperjans, Hermann, et al. 2008), superior parietal areas (7A, 7PC; Scheperjans, Eickhoff, et al. 2008; Scheperjans, Hermann, et al. 2008]), inferior parietal areas (PFop, PFt, PF, PFm, PFcm, PGa; Caspers et al. 2006, 2008), extrastriate visual areas (V3v, V4, V5/hOc3v, hOc4v, hOC5; Malikovic et al. 2007; Rottschy et al. 2007), and the cerebellum (Diedrichsen et al. 2009).

Results

Behavioral Data

In the Free- and the Timed-condition, participants conducted a balanced proportion of right and left button presses (Free: R 42.8 ± 9.2/L 42.4 ± 10.6, $P = 0.41$, R 51.25%; Timed: R 41.8 ± 9.2/L 41.3 ± 9.7, $P = 0.40$, R 50.77). Intervals between feedback offset and self-initiated responses were in average 2.4 s [SD: 1.66 s] and featured a strongly skewed normal distribution (cf. Fig. 2 + Supplementary Fig. S1). Response times in the Timed-condition (mean (*M*): 412 ms, SD: 124 ms) were not different from reaction times in the No Choice-condition (*M*: 436 ms, SD: 77 ms; $P = 0.203$). The error rate in the No Choice-condition was on average 1.51% (SD: 1.87%) and did not differ between button presses with the right or left hand ($P = 0.17$).

Imaging Data—Movement-Related Neural Activity

Dominant right hand movements contrasted to the left hand independent of condition ($R_{all} \cap [R_{free} > L_{free}] \cap [R_{timed} > L_{timed}] \cap [R_{no} > L_{no}]$; Fig. 3) revealed one cluster of activation in the contralateral primary motor (anatomical labeling: Areas 4a and 4p) and somatosensory cortices along the postcentral gyrus (Areas 3b, 3a, 1, 2) and a second in the ipsilateral cerebellum (Lobule V and VI). As expected, responses of the left nondominant hand ($L_{all} \cap [L_{free} > R_{free}] \cap [L_{timed} > R_{timed}] \cap [L_{no} > R_{no}]$) produced a virtually mirror-reversed pattern of activity including an additional activation cluster in the right parietal operculum (OP 1) and the adjacent posterior insula cortex (Ig2).

In order to identify regions that were constantly active throughout all conditions, that is, areas involved in performing hand movements independently of movement side and mode of

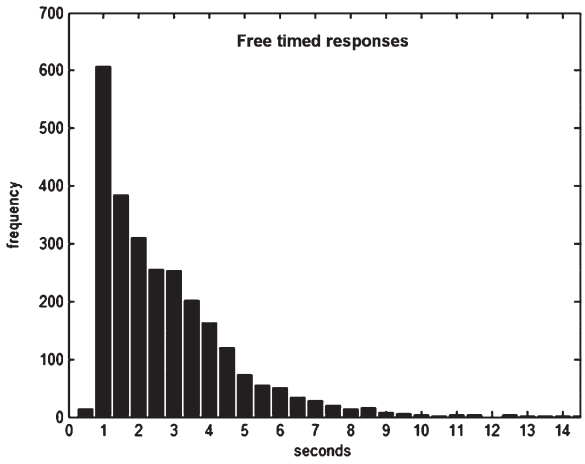

Figure 2. Response time distribution of ~3000 responses after feedback offset in the "Free"-condition.

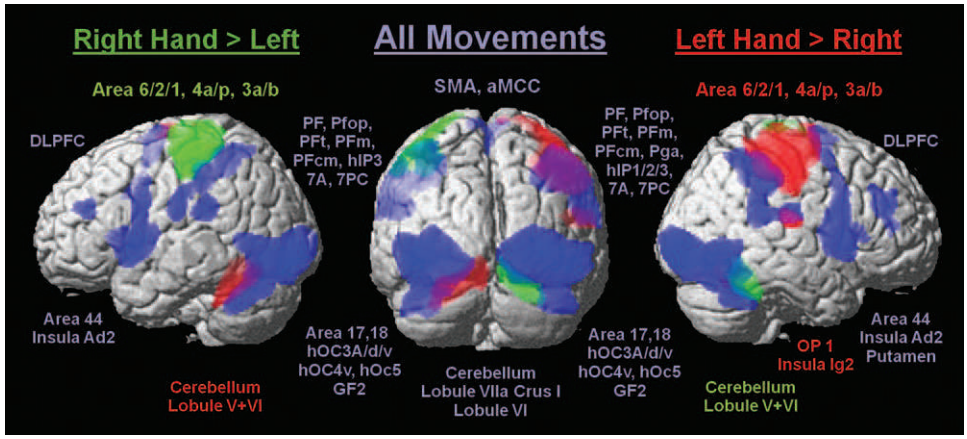

Figure 3. Significant BOLD signal increases in all 3 conditions due to movements of the right hand (green), left hand (red), and both hands (blue) relative to baseline with cytoarchitectonic informed anatomical labeling ($P < 0.05$, cluster level FWE).

movement initiation (core motor areas), a conjunction analysis over all conditions, that is, all 6 regressors, was performed. This analysis revealed a widespread bilateral network consisting of striate (V1/Area 17), extrastriate visual (V2/Area 18; V3/hOC3A, hOC3d, and hOC3v; V4/, hOC4v; V5/hOc5), fusiform gyrus (GF2), somatosensory (Area 2, OP 1 and OP 4) cortices, SMA (Area 6), posterior MCC, area 44, insula (extending into putamen on the right), cerebellum (Lobule VIIa Crus I, Lobule VI), middle frontal gyrus (DLPFC), and inferior (IPL/Area PFop, PFt, PF, PFm, PFcm, and right PGa) together with superior parietal lobule (SPL/Area 7A and 7PC) extending into intraparietal sulcus (IPS/Area hIP3 and right hIP1, hIP2).

Imaging Data—Movement Selection Network

To precisely trace each effect of interest (what- or when-component), we conducted an analysis of all simple main effects between conditions (for MNI coordinates of significant activations, see Supplementary Material) and subsequently computed conjunctions of all contrasts including the specific effect of interest. Although this approach is statistically more conservative than using the main effects only, the mere difference was smaller activation clusters in the more complex conjunctions. Neural effects of the selection to move the left or right hand (what) were localized by contrasting activation in those conditions where the hand to be moved could be freely chosen by the subjects, to those where the hand was visually cued ([Timed > No Choice] ∩ [Free > No Choice]; Fig. 4*A*). This analysis revealed increased activation in medial frontal cortex in a region comprising the pre-SMA extending into aMCC. Bilateral activation was observed in the dorsal premotor (dPMC, Area 6) and the dorsolateral prefrontal cortices (DLPFC: middle frontal gyrus expanding to left Area 45). Bilateral activation was also found in the inferior parietal lobules (IPL/left Area PF, right Area PFm) extending into anterior intraparietal sulcus on the left (IPS/left Areas hIP1 and hIP2). There was no significant effect of movement laterality, which was specific to the Timed-condition only (right hand: [R_{timed} > L_{timed}] ∩ [Timed > No Choice]; left hand: [L_{timed} > R_{timed}] ∩ [Timed > No Choice]).

The reverse contrast testing for areas with increased activity in the No Choice-condition compared with both Free and Timed did not yield significant results. Testing the conditions individually, only the No Choice- against the Timed-condition revealed bilaterally enhanced activity at the temporooccipital junction including V5 (Area hOC5).

Imaging Data—Movement Timing Network

The free determination of the point in time when to execute a particular movement was the exclusive feature of the Free-condition. To dissociate the neural effects of internal timing from the effects of movement choice, we contrasted the Free- against the Timed-condition in conjunction with the Free- against the No Choice-condition ([Free > Timed] ∩ [Free > No Choice]; Fig. 4*B*). Effects of timing selection independent from the used hand were bilaterally found in superior parts of the SMA (Area 6) and the aMCC. Bilateral involvement was also significant for area 44 including anterior insula, anterior putamen, globus pallidus, and DLPFC (middle frontal gyrus). The parietal cortex showed enhanced activity in IPS and IPL (Areas hIP2 and PF), which was more pronounced in the right hemisphere (Areas hIP1, hIP3, PFm) extending into the superior parietal lobule (SPL/right Area 7PC). Unilateral activation due to movement timing was present in the left cerebellum (Lobule VIIa Crus I and Lobule VI).

The reverse contrast (Timed > Free), however, did not yield any significant neuronal activation.

Imaging Data—Comparison of Movement Selection and Timing

The comparison of activation patterns associated with movement selection (what) and those for internal timing of

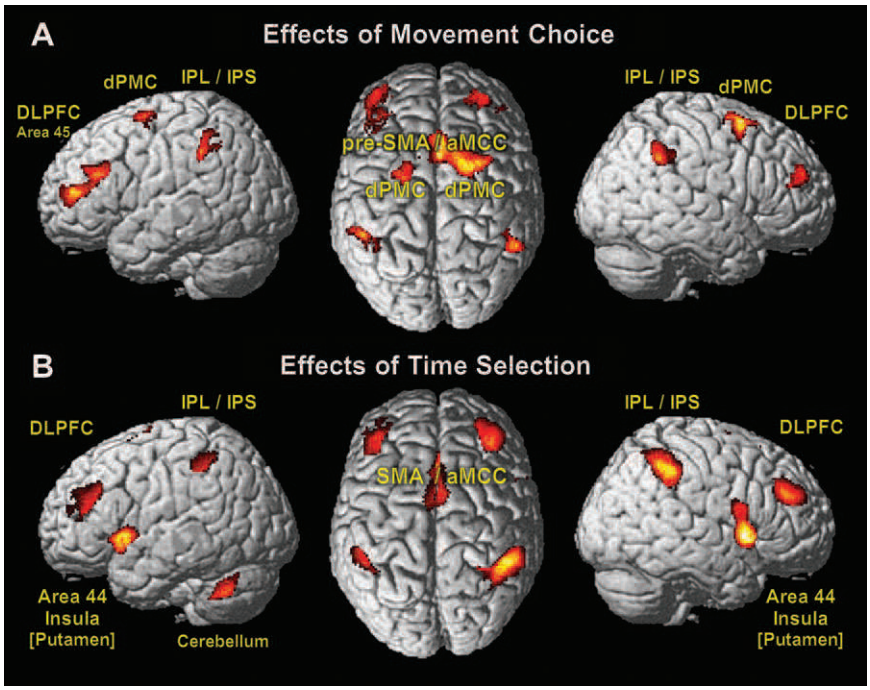

Figure 4. Significant effects of movement choice (what; *A*) and time selection (when; *B*) with macroanatomic labels ($P < 0.05$, cluster level FWE).

movement execution (when) revealed that both factors engaged the aMCC, the IPL/IPS, and the DLPFC in both hemispheres (Fig. 5). For movement selection, the contribution of IPL/IPS was rather symmetrical between the hemispheres, while for movement timing, IPL/IPS activation appeared to have a tendency of right hemispherical lateralization. In contrast, within the DLPFC, movement selection showed a left hemispheric dominance, while internal timing seemed distributed quite similar. Furthermore, prefrontal activation relating to timing selection was located more superior and posterior to activation due to movement selection. A conjunction analysis between movement selection and timing ([Free > Timed] ∩ [Timed > No Choice] ∩ [Free > No Choice]) revealed a common focus of activity in the aMCC. A closer look on the 6 parameter estimates (right and left hand in each condition = 2 × 3; Fig. 6) at the peak voxel of the aMCC demonstrated that the activation of the aMCC was proportional to the "intentional load" represented by the number of selection components (what/when) necessary for movement initiation. That is, while reactive movements did not evoke any additional activation in the aMCC compared with baseline, the selection of hand in the Timed-condition evoked a significant neuronal response, which even increased significantly when the selection of execution timing was additionally required in the Free-condition. Only the aMCC was activated in this highly specific manner, that is, only the aMCC featured the specific profile of activity indicating a key role in internally specified (generated) actions: (Free > Timed > Reactive = Baseline). To test whether other regions were involved solely in the internal selection of movements or timing, the effect of reactive movements (No Choice-condition vs. baseline; $P < 0.05$, cluster level FWE) was used as an exclusive mask for the effects of movement selection and of movement timing. This analysis thus aimed at revealing regions showing an effect of movement or timing choice while not showing activity related to reactive movements. (Supplementary Fig. S2). The masked what'-contrast (movement selection) revealed that pre-SMA and bilateral dPMC were exclusively activated in relation to the internal selection of movements but not by reactive movements as were parts of bilateral DLPFC and of left IPL/IPS (IPL/Area PF; IPS/Area hIP1 and hIP2). Masking the when-contrast (timing selection) showed activation in bilateral anterior putamen and globus pallidus as well as parts of left DLPFC and an inferior aMCC in movement timing, but no significant activation evoked by reactive movements.

Discussion

In this study, we manipulated movement selection and timing within the same paradigm introducing for the first time actual

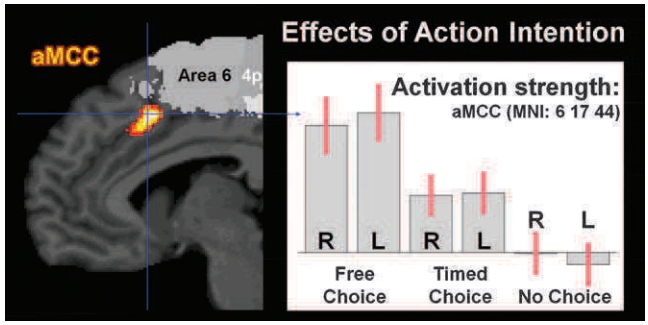

Figure 6. Parameter estimates of the aMCC for right (R) and left (L) hand movements in 3 experimental conditions (confidence intervals in red). Neuronal activity was increased in the "Timed"- (what) and even higher in the "Free"-conditions (what + when) compared with the "No Choice"-condition.

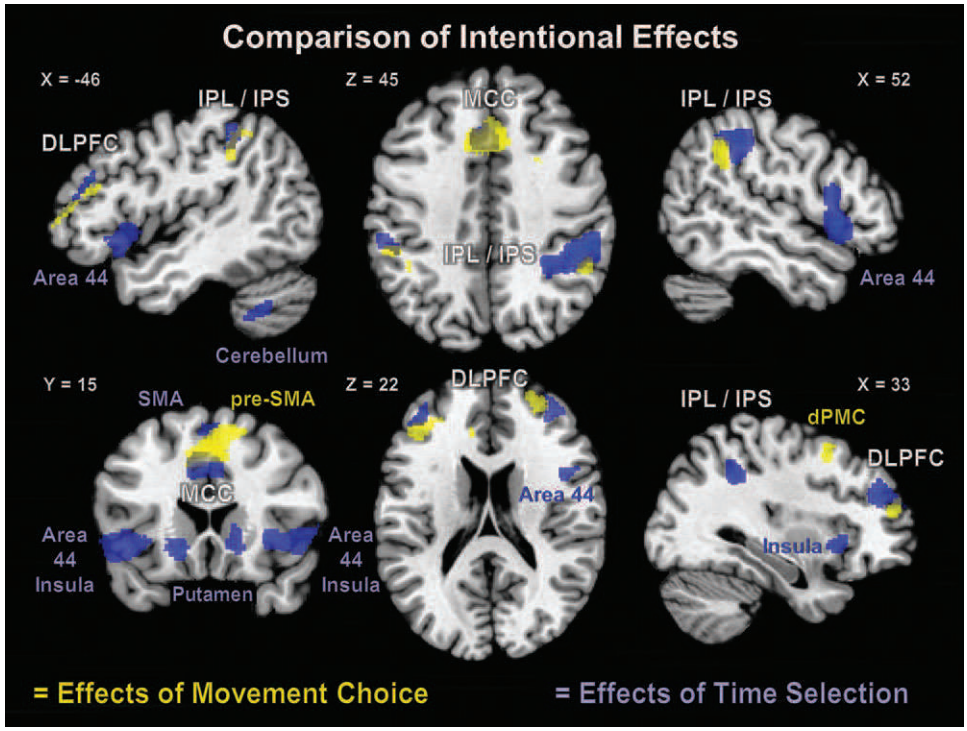

Figure 5. Comparison of intentional effects with regions of activation due to movement choice (what in yellow) and time selection (when in blue) marked with macroanatomic labels ($P < 0.05$, cluster level FWE). Those regions that feature conjoint activation of "what" and "when" are labeled in using white fond.

free determination of a time point for movement initiation in addition to the free choice of which movement to enact. More specifically, in our free condition, subjects had to choose between a left and a right hand movement to be initiated on a not-cued point in time but rather spontaneously, that is, self-initiated. Importantly, the current design allowed us to ensure a high degree of comparability between the conditions, as we controlled for visual stimulation (by introducing the feedback in the Free-condition) and used the (randomized) timing and response parameters from the self-initiated condition for the subsequent reactive and forced-choice blocks. Finally, we applied an event-related design with the trigger set on the movements to be certain to effectively analyze neural activity related to internally specified movement initiation. By focusing on spontaneous movement initiation and parceling out activity due to visual stimulation and movement execution, the current study allowed to specifically isolate the what and when components of internally specified movements in an ecologically valid paradigm.

The choice of "what to do" evoked robust activity in the pre-SMA extending into the aMCC, along with bilateral dPMC, which are all involved in movement selection and execution (Haggard 2008). The choice of when to act reliably increased neural activity in the aMCC, together with bilateral area 44, anterior insula, SMA, putamen, globus pallidus, and left cerebellum, all associated with internal timing and sequencing of movements (Wiener et al. 2010). Both selection and timing of movements engaged adjacent regions in the parietal and prefrontal cortices frequently associated with spatial attention and behavioral planning (Corbetta and Shulman 2002). The key finding of this study is that the aMCC was the only region that featured increasing activity with more intentional components during movement initiation. Thereby, we provide additional evidence for a crucial contribution of the aMCC to intentional motor control (Paus 2001).

The What of Self-Initiated Movements

The decision of what to do, that is, the free selection of a left or right index finger flexion recruited pre-SMA including aMCC together with dPMC. Chouinard and Paus (2006, 2010) pointed out the importance of the dPMC in response selection. As demonstrated in numerous previous studies, pre-SMA and aMCC feature increases of activity during internal selection and initiation of movements (Deiber et al. 1999; Cunnington et al. 2002, 2003; Lau, Rogers, Haggard, et al. 2004; Cunnington 2005; van Eimeren et al. 2006). Lau, Rogers, Ramnani, et al. (2004) and Lau et al. (2006) showed that the free selection of responses is tightly associated with the pre-SMA, whereas response conflicts triggered activity increase especially in the aMCC. On the other hand, Nachev et al. (2007) demonstrated that pre-SMA injury can lead to a selective deficit in the ability to inhibit a response. Likewise, a recent meta-analysis by Swick et al. (2011) highlighted the role of the pre-SMA for response inhibition in both STOP-Signal and GO/ NO-GO tasks. Hence, there is strong evidence for inhibition of behavior rather than selection as an essential function of the pre-SMA. Yet, following the argument of Mostofsky and Simmonds (2008) and Simmonds et al. (2008), response inhibition can be conceptionalized as selection to withhold a specific response, that is, selective movement inhibition (Coxon et al. 2009). Consequently, inhibition and selection can be seen as 2 sides of the same coin (Mostofsky and Simmonds 2008). Well in line is the predominant role of the pre-SMA in resolving response competition (Ullsperger and von Cramon 2001; Lau et al. 2006) when the selection of one response and the inhibition of another are simultaneously required to yield coherent behavior. Thus, the pre-SMA seems to fulfill a gating function in intentional motor control by inhibiting stimulus-driven reactive behavior as well as triggering non-cued movements, as for instance necessary in asynchronous (syncopated) movement pacing to rhythmic cues (Mueller et al. 2007). Consequently, our data suggest that the pre-SMA is specifically associated with the what-component of self-initiated movements conceived as selective behavior in contrast to stimulus-driven reactive behavior, that is, selective motor initiation.

The When of Self-Initiated Movements

The decision when to act, that is, the free timing of a finger flexion, yielded activity increase in aMCC, superior SMA, and left cerebellum as well as bilateral involvement of area 44 extending to anterior insula, putamen, and globus pallidus. The interpretation of this result is limited in so far that the free timing of movement initiation (when) was assessed only conjointly with the free hand choice (what). Hence, some aspects of free movement timing may not be captured by the current subtraction design. Instead, the conducted experiment was especially designed to maximize comparability between conditions and thereby between what and when of self-initiated movements. Importantly, studies specifically examining the free timing of predefined movements previously demonstrated the association of aMCC and SMA activity with self-paced movement initiation (Ball et al. 1999; Deiber et al. 1999; Jenkins et al. 2000). The SMA, however, is also involved in externally triggered movements (Romo and Schultz 1987; Thaler et al. 1988; Picard and Strick 2003; Grefkes et al. 2008) and mediated by the type of movement (Deiber et al. 1999; van Eimeren et al. 2006; Bortoletto and Cunnington 2010).

Following Lewis and Miall (2003), intentional movement timing may be scaled in subsecond and in suprasecond intervals relating to more spontaneous (automatic) and more cognitively controlled timing, respectively. Both timing processes are jointly engaged in intentional movement initiation. In a voxel-wise meta-analysis accounting for 45 imaging experiments, Wiener et al. (2010) found the SMA and the right area 44 as part of a core network mediating timing in the brain. Unsurprisingly, the speech dominant left area 44 seemed restricted to subsecond perceptual timing (Wiener et al. 2010). Regarding manual control as demanded in this study, area 44 is involved in execution timing, that is, delay of hand postures (Makuuchi 2005) and in response selection and inhibition on base of internal representations (Kan and Thompson-Schill 2004; Zhang et al. 2004). In the same meta-analysis, putamen, globus pallidus, and cerebellum were consistently implicated in rather automated subsecond timing, whereas bilateral insula demonstrated significant contribution to more cognitive suprasecond timing (Wiener et al. 2010). In self-initiated movements, the execution of nonroutine movement pattern was demonstrated to specifically activate bilateral putamen (Francois-Brosseau et al. 2009) and globus pallidus (Jankowski et al. 2009). Also in line with our results, lobule VII crus I of the left cerebellum was found to be especially sensitive to timing in the context of interval coding (Harrington et al. 2004). Furthermore, the

anterior insula is thought to play an essential role in evaluating the consequences of intentional action (Brass and Haggard 2010). Taken together, our results reflect previous findings, associating area 44, and anterior insula with more cognitive internal timing of actions and SMA, basal ganglia, and left cerebellum with rather automatic timing and coordination of movement execution (Witt et al. 2008). As hypothesized, parts of the basal ganglia, in particular, bilateral anterior putamen and globus pallidus are involved in intentional movement timing in contrast to cued timing. In line with our hypothesis, decreased control of motor timing in Parkinson's disease may be explained at least partly by impaired activation of putamen, SMA, right insula, and aMCC (Playford et al. 1992; Jahanshahi et al. 1995) as well as by decreased functional connectivity of left putamen and right insula with the pre-SMA (Wu et al. 2011).

Intentional Movement Initiation

The aMCC was sensitive to what and when decisions in self-initiated movements and showed additive effects when both were combined. In particular, the aMCC (MNI coordinates: x = −3, y = 18, z = 42) featured not only increased activity for internal movement selection (what) over reactive movements but even higher levels of activation for additional internal timing of movement execution (when). This additive effect of what and when provides strong evidence for the interdependence of both components on the neuronal level, as suggested by Krieghoff et al. (2009). This characteristic is well in line with the current view of the aMCC as a brain area crucially involved in various cognitive control functions (cf. Shackman et al. 2011). On one hand, this area accounts for conflict processing, that is, conflict monitoring (Botvinick et al. 2004; Carter and van Veen 2007) and conflict anticipation (Murtha et al. 1996; Brown and Braver 2005). Furthermore, the aMCC is essentially involved in higher order cognitive processes, such as reward-guided action selection (Bush et al. 2002; Rushworth et al. 2004; Walton et al. 2004) and the implementation of task sets (Dosenbach et al. 2006, 2007). Recently, Aarts et al. (2008) provided evidence for a more fundamental role of the aMCC in anticipatory control, that is, preparatory activity reflecting control adjustments in relation to an upcoming task, independent of anticipated conflict or error likelihood. Our findings that the very simple task of choosing a finger to flex and the moment to do so (without any anticipation of conflict or reward) likewise evoked robust activation in the aMCC supports this view. Furthermore, anticipation should not be any factor in the Free-condition as there is no upcoming event but rather the intentional self-specified decision to perform a movement. We would thus conclude that the role of the aMCC may not necessarily be related to anticipatory control, even though there is always the implicit expectation of sensory consequences in intentional action (Fink et al. 1999). We would thus interpret our findings as evidence for the view (Paus 2001) that the aMCC is situated in a strategic position to regulate the interaction between high-level cognition and motor control, which is also supported by the current knowledge on the structural and functional organization of the primate anterior cingulate cortex (Hoshi et al. 2005). Overall, our results thus strongly suggest a key role of the aMCC in intentional motor control. Its putative function as a hub for the implementation of intentions into actions in turn may provide the foundation for other cognitive functions frequently associated with this area.

Behavioral Planning

"Willed action" is typically related to the PFC (Frith et al. 1991; Hyder et al. 1997) as it was suggested by most of the studies on intentional action mentioned above. Studies in nonhuman primates showed that lateral PFC is primarily involved in behavioral planning and less in the specification of motor aspects of behavior (Tanji et al. 2007). Likewise, the lateral PFC in humans preferentially contributes to attentional and working memory processes involved in the preparation rather than the initiation of the actual movements (Wiese et al. 2005, 2006). Using electroencephalography and fMRI in one study, Bortoletto and Cunnington (2010) directly demonstrated that the lateral PFC plays an important role in determining the timing for movement initiation 1 s prior to self-initiated movements. In their comprehensive review, Tanji and Hoshi (2008) presented evidence for a functional heterogeneity within the lateral PFC. Generally speaking, the ventrolateral part is associated with "first-order" executive processes, such as active retrieval and selection of information, whereas the DLPFC is more involved in "higher order" executive functions, such as monitoring, integration, and manipulation of information. In our study, the what and when of intentional action initiation recruited mainly the DLPFC, which is in line with the concept of intentional actions being rooted in those higher order executive functions. However, no convergence of what and when of self-initiated movements was found within the DLPFC further supporting the notion of a functional heterogeneous DLPFC.

Movement Intentions and Motor Awareness

Intentional movement initiation reliably activates the inferior parietal cortex (cf. Deiber et al. 1999; Jenkins et al. 2000), which seems to be a critical node for the representation of actions and intentions to act (Tunik et al. 2007). In our study, movement selection (what) involved bilateral dPMC and IPS, which conjointly are known as the dorsal attention network (Fox et al. 2006; Corbetta et al. 2008) and are closely linked to control of hand movements (Filimon 2010) and motor imagery (Lorey et al. 2011). Recently, Gallivan et al. (2011) showed that specific movement intentions can be predicted by the spatial activity patterns in these areas. Moreover, although lesions in the inferior parietal cortex do not entail difficulties initiating voluntary actions, they seem to impair awareness of movement intentions (Sirigu et al. 2004). Conversely, direct electrical stimulation of the IPL triggered the strong intention to move a body part and with increased stimulation intensity led to illusory movement awareness (Desmurget et al. 2009). Stimulation on the dPMC, on the other hand, evoked movements without movement intention or motor awareness. Thus, in context of intentional action, the IPL/IPS seem to contribute to movement intention and motor awareness, whereas the dPMC is closer to movement execution.

A Medial and a Lateral Premotor System

Over 2 decades ago, Goldberg (1985) distinguished 2 separate premotor systems based on phylogenetic characteristics, structural connectivity pattern, and functional properties of the areas involved. A medial system consisting of SMA and basal ganglia was associated with internal movement generation. In contrast, external movement generation was associated with a lateral premotor system consisting of the lateral premotor cortex and the cerebellum. In our study, we focused on

internal movement generation and found both the medial and the lateral system involved in this process. In particular, we observed rostral aspects of the bilateral dPMC activity in the internal selection (what) of movements in comparison with external (reactive) movement generation. The cerebellum (Lobule VIIa Crus I, Lobule VI) as the subcortical part of the lateral system was involved in both internal and external movement generation with the left hemisphere showing increased activity for internal timing (when). Likewise, the SMA proper as center of this medial system was involved in both internal and external generation of movements, while its superior aspect moreover increased activity with internal movement timing (when). Furthermore, while absent in external movement generation, the pre-SMA was involved in internal selection (what), whereas the basal ganglia, namely globus pallidus and anterior putamen, were exclusively activated by internal movement timing (when). In contrast, only aMCC was additively recruited by internal movement selection (what) and timing (when) without any activity during the generation of reactive movements. Taken together, our study thus adds evidence for 2 essential modifications of the Goldberg model. First, the lateral system is not exclusively involved in external movement generation but seems to be rather linked to movement selection (what) per se. Second, as proposed earlier (cf. Haggard 2008), the medial premotor system consists of the pre-SMA together with anterior putamen and globus pallidus subcortically. Possibly mediated by aMCC, this medial system seems to play a key role in internal movement generation especially if both what and when of a movement are internally specified.

Conclusion

In this study, we examined intentional movement initiation and directly demonstrated the essential involvement of the aMCC both in internal selection (what) and timing (when) of movements. The pre-SMA is specifically associated with selective motor initiation (what), in which the dPMC seems to account for movement execution. Internal timing (when) relies crucially on bilateral anterior putamen and globus pallidus, which together with the pre-SMA are known as the medial premotor system. Moreover, intentional movement timing seems to rely on a well-distributed timing network comprised of bilateral area 44 and anterior insula for cognitive time processing and SMA, basal ganglia, and cerebellum related to more automated timing of movement execution. In internal movement generation, IPL/ IPS are closely related to movement intention and motor awareness. Finally, we provide additional evidence for a fundamental role of the aMCC in initiating and implementing intentional motor control and thereby translating intentions into actions.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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Notes

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Supplementary Material: Table S1

Macro-anatomic classification	Anatomical label	Side	k =	MNI x / y / z
Free > No Choice				
aMCC	-		15218	-2 / 23 / 39
pre-SMA	Area 6			0 / 18 / 56
SMA	Area 6			2 / 8 / 63
dPMC	Area 6	R		17 / 6 / 62
DLPFC	-			30 / 48 / 29
Broca's Area	Area 44			56 / 11 / 5
	Area 45			*52 / 24 / 8*
Insula	-			36 / 11 / -2
Basal Ganglia	Putamen			17 / 15 / -6
	Globus Pallidus			*19 / 4 / 0*
dPMC	Area 6	L	810	-20 / 5 / 66
Broca's Area	Area 44	L	4561	-50 / 14 / 2
Insula	-			-39 / 11 / -3
Basal Ganglia	Putamen			-17 / 18 / -5
	Globus Pallidus			-18 / 5 / -3
DLPFC	-	L	3300	-39 / 41 / 27
Broca's Area	Area 45			*-42 / 26 / 27*
IPL	PF	R	4832	53 / -39 / 47
	PFm			50 / -48 / 53
	PGa			45 / -63 / 50
IPS	hIP1			41 / -41 / 36
	hIP2			*44 / -46 / 49*
	hIP3			32 / -48 / 42
SPL	7P			15 / -72 / 54
	7A			*38 / -55 / 54*
	7PC			*42 / -55 / 67*
IPL	PF	L	2120	-50 / -44 / 53
	PFm			*-45 / -52 / 47*
IPS	hIP1			-39 / -44 / 41
	hIP2			-50 / -42 / 47
	hIP3			*-40 / -40 / 41*
	Area 2			*-48 / -46 / 53*
Cerebellum	Lobule VIIa Crus I	R	690	35 / -60 / -35
Cerebellum	Lobule VIIa Crus I	L	1498	-35 / -57 / -36
	Lobule VI			*-32 / -55 / -33*
Free > Timed				
SMA	Area 6		605	2 / 2 / 68
aMCC	-		1385	0 / 18 / 41
Insula	-	R	2116	48 / 9 / 0
Broca's Area	Area 44			*50 / 8 / 17*
Basal Ganglia	Putamen	R	780	20 / 6 / -5
	Globus Pallidus			*19 / 4 / 0*
Insula	-	L	2256	-41 / 14 / -3
Broca's Area	Area 44			*-52 / 14 / 1*
Basal Ganglia	Putamen			-17 / 11 / -6
	Globus Pallidus			-18 / 5 / -3
Cerebellum	Lobule VIIa Crus I	L	857	-35 / -56 / -35
	Lobule VI			*-31 / -55 / -34*
DLPFC	-	R	891	41 / 42 / 29
DLPFC	-	L	580	-41 / 39 / 24
IPL	PF	R	2172	53 / -41 / 45
	PFm			50 / -47 / 53
IPS	hIP1			41 / -41 / 36
	hIP2			44 / -42 / 44
	hIP3			32 / -48 / 42
SPL	7PC			*44 / -46 / 58*
IPL	PF	L	324	-53 / -38 / 51
IPS	hIP2			-50 / -42 / 54
Timed > No Choice				
aMCC	-		3669	-8 / 20 / 38
pre-SMA	Area 6			0 / 17 / 50
dPMC	Area 6	R		20 / 3 / 62
dPMC	Area 6	L	552	-20 / -2 / 63
DLPFC	-	R	573	32 / 47 / 21
DLPFC	-	L	1516	-39 / 47 / 11
Broca's Area	Area 45			*-45 / 29 / 22*
IPL	PFm	R	522	51 / -50 / 36
IPL	PF	L	505	-56 / -41 / 38
IPS	hIP1			-39 / -45 / 39
	hIP2			-51 / -41 / 39

Macro-anatomic classification	Anatomical label	Side	k =	MNI x / y / z
No Choice > Timed				
V5	hOC5	R	1130	53 / -66 / 6
V5	hOC5	L	789	*-42 / -69 / 15*
'What' [(Timed > No Choice) ∩ (Free > No Choice)]				
aMCC	-		3148	-8 / 20 / 38
pre-SMA	Area 6			0 / 17 / 50
dPMC	Area 6	R		20 / 3 / 62
dPMC	Area 6	L	348	-20 / -2 / 65
DLPFC	-	R	370	32 / 47 / 21
DLPFC	-	L	1193	-38 / 47 / 12
Broca's Area	Area 45			-41 / 35 / 15
IPL	PFm	R	505	51 / -50 / 36
IPL	PF	L	498	-57 / -39 / 36
IPS	hIP1			-39 / -45 / 39
	hIP2			-51 / -41 / 39
'What' [(Timed > No Choice) ∩ (Free > No Choice)] **exclusively masked with: No Choice**				
pre-SMA	Area 6		3141	0 / 17 / 50
dPMC	Area 6	R		20 / 3 / 62
dPMC	Area 6	L	348	-20 / -2 / 65
DLPFC	-	R	337	32 / 47 / 21
DLPFC	-	L	1054	-38 / 47 / 12
Broca's Area	Area 45			-41 / 35 / 15
IPL	PF	L	382	-57 / -39 / 36
IPS	hIP1			-39 / -45 / 38
	hIP2			-51 / -41 / 39
'When' [(Free > Timed) ∩ (Free > No Choice)]				
SMA	Area 6		583	2 / 2 / 68
aMCC	-		1385	3 / 17 / 39
Broca's Area	Area 44	R	2026	50 / 8 / 17
Insula	-			48 / 9 / 0
Broca's Area	Area 44	L	1142	-62 / 12 / 5
Insula	-			-41 / 14 / -3
Basal Ganglia	Putamen	R	737	20 / 6 / -5
	Globus Pallidus			*19 / 4 / 0*
Basal Ganglia	Putamen	L	915	-17 / 11 / -6
	Globus Pallidus			-18 / 5 / -3
Cerebellum	Lobule VIIa Crus I	L	828	-35 / -56 / -35
	Lobule VI			*-31 / -55 / -34*
DLPFC	-	R	891	41 / 42 / 29
DLPFC	-	L	580	-41 / 39 / 24
IPL	PF	R	2145	53 / -41 / 45
	PFm			50 / -47 / 53
IPS	hIP1			41 / -41 / 36
	hIP2			44 / -42 / 44
	hIP3			32 / -48 / 42
SPL	7PC			*44 / -46 / 55*
IPL	PF	L	313	-53 / -38 / 51
IPS	hIP2			-50 / -42 / 54
'When' [(Free > Timed) ∩ (Free > No Choice)] **exclusively masked with: No Choice**				
MCC	-		1280	3 / 17 / 39
Basal Ganglia	Putamen	R	568	20 / 6 / -5
	Globus Pallidus			*19 / 4 / -5*
Basal Ganglia	Putamen	L	812	-17 / 11 / -6
	Globus Pallidus			-18 / 5 / -3
DLPFC	-	L	330	-45 / 38 / 24
'What & When' [(Free > Timed) ∩ (Timed > No Choice) ∩ (Free > No Choice)]				
aMCC	-		555	-3 / 18 / 42

Table S1: Effects of contrasts (>) and conjunctions (∩)

Table shows MNI-coordinates (x y z) of peak activation in each cytoarchitectonic area within activated clusters (size: k) as assigned by the SPM Anatomy toolbox (Eickhoff SB et al. 2005; Eickhoff SB et al. 2006; Eickhoff SB et al. 2007). If there was no peak within a certain area a coordinate in the middle of that anatomical area is reported and italicized in the table. All results are FWE-corrected on the cluster level (extend threshold: k = 313) with $p < 0.05$.

Supplementary Figures Legend

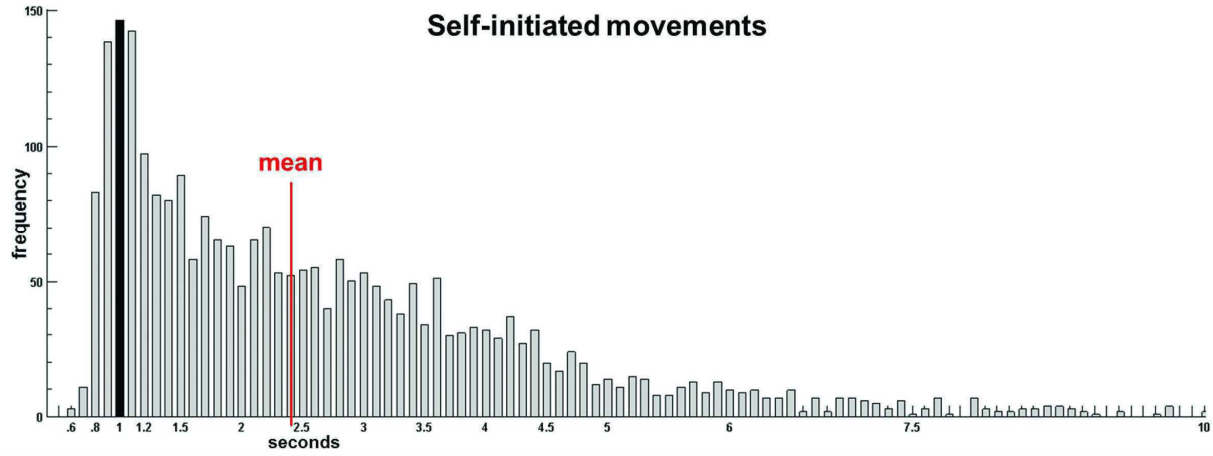

Figure S1: Self-initiated Movements

Skewed normal distribution of response times in the '*Free*'-condition, i.e., intervals between feedback offset and self-initiated responses. The histogram includes 2982 responses (mean: 2.4 s; standard deviation: 1.66 s) with maximum frequency at 1 s and maximum time at 15 s.

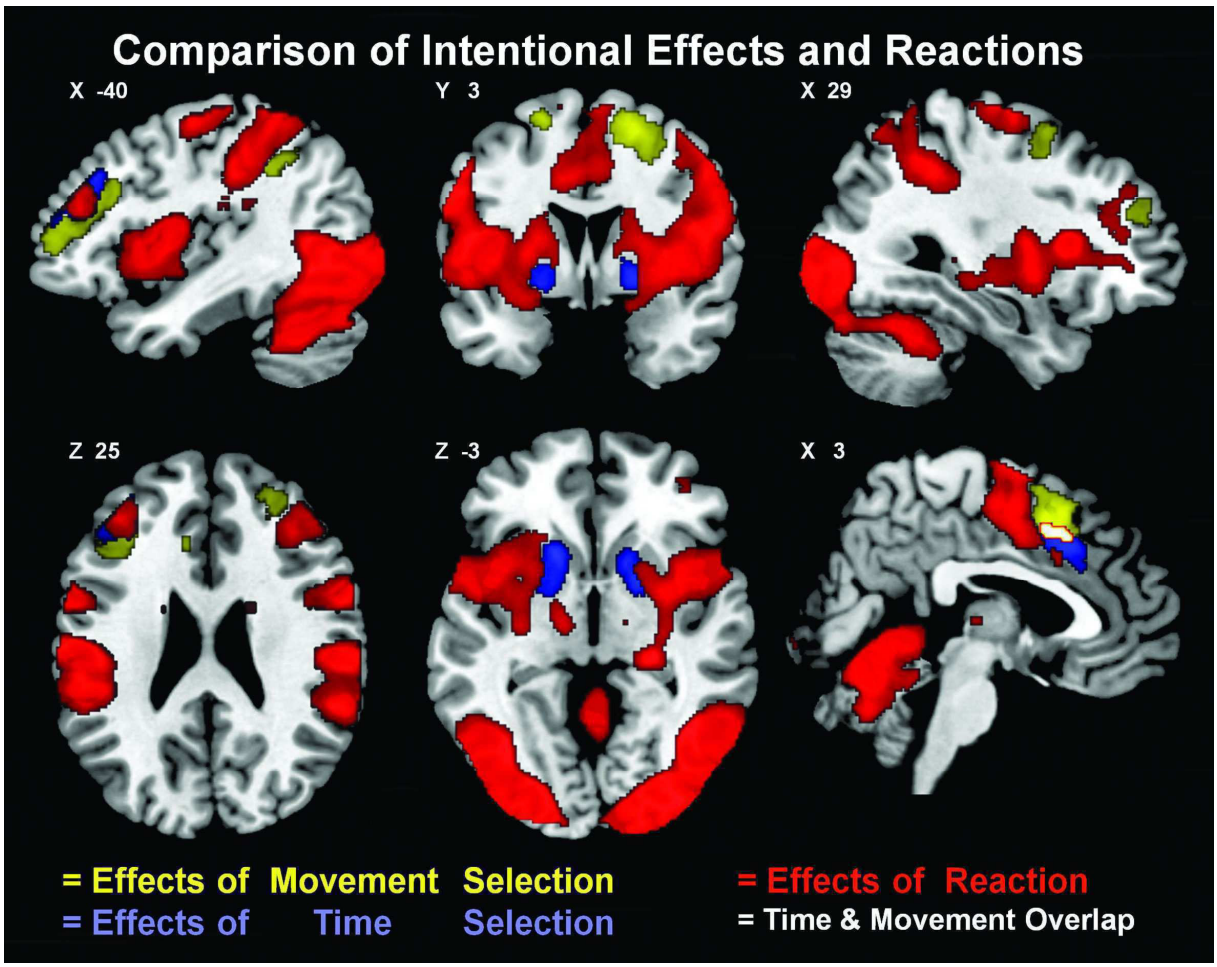

Figure S2: Comparison of intentional effects and reactions

The Figure shows areas exclusively activated for internally specified actions in contrast to effects of reaction. Therefore, the reaction main effect (red; 'No Choice'-condition vs. baseline) was applied as exclusive mask for the effects of action selection (yellow) and of movement timing (blue). All results are cluster level FWE corrected with $p < 0.05$.

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Erklärung § 5 Abs. 1 zur Datenaufbewahrung

Hiermit erkläre ich, dass die dieser Dissertation zu Grunde liegenden Originaldaten in der Klinik für Psychiatrie, Psychotherapie und Psychosomatik des Universitätsklinikums Aachen (Hoffstaedter et al., 2012) sowie im Institut für Neurowissenschaften und Medizin des Forschungszentrums Jülich (Hoffstaedter et al. 2013) hinterlegt sind.

Erklärung gemäß § 5 Abs. (1) und (2), und § 10 Abs. (3) 12. der Promotionsordnung

Hiermit erkläre ich, Herr Felix Hoffstaedter an Eides statt, dass ich den wesentlichen Anteil an der Publikation:

Felix Hoffstaedter, Jan Sarlon, Christian Grefkes, Simon B. Eickhoff: Internally vs. externally triggered movements in patients with major depression, (2012). *Behavioural Brain Research* (2012) 228(1):125-132

geleistet habe.

Die Anteile an der Arbeit waren wie folgt:

F. Hoffstaedter:	Durchführung sämtlicher Experimente und Erstellung des Manuskriptes
J. Sarlon:	Rekrutierung von Patienten sowie klinische Diagnostik, Mithilfe bei der Erstellung des Manuskripts
C. Grefkes:	Konzeption der Arbeit, Diskussion der Ergebnisse, Korrektur des Manuskripts
S. B. Eickhoff:	Studiendesign, Betreuung der Arbeit, Korrektur des Manuskriptes

Aus diesem wesentlichen Anteil ergibt sich selbstverständlich die Stellung als Erstautor.

Als Doktorvater und Letzt-Autor bestätige ich die Angaben von Herrn Felix Hoffstaedter.

Univ.-Prof. Dr. med. Simon B. Eickhoff

Ich schließe mich der Erklärung von Univ.-Prof. Dr. med. Simon B. Eickhoff als Koautor an.

J. Sarlon C. Grefkes

Erklärung gemäß § 5 Abs. (1) und (2), und § 10 Abs. (3) 12. der Promotionsordnung

Hiermit erkläre ich, Herr Felix Hoffstaedter an Eides statt, dass ich den wesentlichen Anteil an der Publikation:
Felix Hoffstaedter, Christian Grefkes, Karl Zilles, Simon B. Eickhoff: The "what" and "when" of self-initiated movements, *Cerebral Cortex* (2013) 23(3):520-530.

geleistet habe.

Die Anteile an der Arbeit waren wie folgt:

F. Hoffstaedter:	Durchführung sämtlicher Experimente und Erstellung des Manuskriptes
C. Grefkes:	Studiendesign, Diskussion der Ergebnisse, Korrektur des Manuskripts
K. Zilles:	Konzeption der Arbeit, Diskussion der Ergebnisse, Korrektur des Manuskriptes
S. B. Eickhoff:	Studiendesign, Betreuung der Arbeit, Korrektur des Manuskriptes

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C. Grefkes K. Zilles